NEW AND NONOFFICIAL REMEDIES

1930

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American medical association. Council
on pharmacy and chemistry.

NEW AND NONOFFICIAL REMEDIES, 1930

Containing Descriptions of the

Articles Which Stand Accepted by the Council
on Pharmacy and Chemistry of the
American Medical Association
on January 1, 1930

American Medical Association
535 North Dearborn Street
CHICAGO

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American Medical Association
535 North Dearborn Street
CHICAGO

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PREFACE

New and Nonofficial Remedies is a book in which are listed and described the articles that stand accepted by the Council on Pharmacy and Chemistry of the American Medical Association on January 1 of the year of publication. The descriptions of accepted articles are based in part on investigations made by, or under the direction of, the Council, and in part on evidence or information supplied by the manufacturer or his agents. Statements made by those commercially interested are examined critically and admitted only when they are supported by other evidence or when they conform to known facts.

The following articles have been omitted by action of the Council during 1929 because they conflict with the rules that govern the recognition of articles or because their distributors did not present evidence to demonstrate their continued eligibility: Siomine (Pitman-Moore Co.); Loeflund's Malt Extract with Cod Liver Oil (Britt, Loeffler & Weil); Psyllium Seed-Richards (Richards, Inc.); all digestive enzyme preparations for internal use, which include Elizir of Enzymes (Armour); Essence of Pepsine-Fairchild, Gastron, Diazyme Glycerole, Holadin (Fairchild Bros. & Foster), and Panase (Frederick Stearns & Co.); all desiccated ovarian preparations, which include Ovarian Substance-Armour, Ovarian Substance Desiccated-P. D. & Co., Ovarian Substance-P.-M. Co. Desiccated, Ovarian Substance-Wilson, Whole Ovary-H. W. & D., Whole Ovary-Lederle, Ovarian Residue-H. W. & D., Ovarian Residue-Lederle, Ovarian Residue-P.-M. Co. Desiccated, Ovarian Residue Desiccated-P. D. & Co., Ovarian Residue-Wilson, Corpus Luteum-Lederle, Corpus Luteum-P.-M. Co. Desiccated, Corpora Lutea Desiccated-P. D. & Co., Desiccated Corpus Luteum-Armour, Desiccated Corpus Luteum-Wilson, Lutein-H. W. & D.; all desiccated pituitary preparations, which include Desiccated Pituitary Body-Armour, Desiccated Pituitary Substance (Anterior Lobe)-Armour, Pituitary Substance-P.-M. Co. Desiccated, Anterior Pituitary Desiccated-Lederle, Posterior Pituitary Desiccated-Lederle, Whole Pituitary Desiccated-Lederle, Pituitary Body Anterior Lobe Desiccated-Mulford, Desiccated Pituitary Substance (Posterior Lobe)-Armour, Posterior Pituitary-P.-M. Co. Desiccated; all antistreptococcus serums, which include Antistreptococcic Serum (Gilliland), Antistreptococcus Serum Polyvalent (Lederle), Antistrepto-

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coccic Serum (N. D. Co.), Antistreptococcic Serum (Mulford), Antistreptococcic Serum (P. D. & Co.), Antistreptococcic Serum (Squibb); and all pneumococcus vaccines, which include Pneumococcus Antigen (Lilly), Pneumococcus Vaccine Immunizing (Gilliland), Pneumococcus Vaccine (Lederle), Pneumococcus Vaccine Prophylactic (Lilly), Pneumococcus Vaccine (N. D. Co.), Pneumococcus Vaccine (4 Types) (P. D. & Co.), Pneumococcus Immunogen (P. D. & Co.), Pneumococcus Vaccine (Squibb).

The following articles have been omitted as being off the market: Yellow Dock Pollen Extract and Yellow Dock Pollen Extract Concentrated (Cutter Laboratory); Tuberculin T. R. Concentrated Human Strain, Tuberculin B. E. Concentrated Human Strain, and Tuberculin B. F. Concentrated Human Strain (Eli Lilly & Co.); Maltine Malt Soup Extract (The Maltine Co.); Vi-Mal-Dex Orange (Merrell-Soule Co.); Novocain Base (H. A. Metz Laboratories, Inc.); Erysipelas Streptococcus Antitoxin-Mulford, Sterile Solution of Dextrose (d-Glucose) 50 cc. Double End Vial, Sterile Solution of Dextrose (d-Glucose) 20 cc. Ampule, Sterile Solution of Dextrose (d-Glucose) 50 cc. Ampule and Protan and Opium Tablets No. 2 (H. K. Mulford Co.); Capsules Solution Silver Nitrate 2 Per Cent (Parke, Davis & Co.); Solution of Arsphenamine (E. R. Squibb & Sons); and Gentian Violet Capsules-Swan-Myers 1 Grain (Swan-Myers Co.). Mead's Powdered Lactic Acid Milk (Acidified with Lactic Acid U. S. P.), Mead's Powdered Lactic Acid Milk Non-Curdling No. 2, and Mead's Powdered Lactic Acid Milk (Cultured) were omitted and referred to the Committee on Foods.

The grouping together of articles having similar composition or actions is continued in this edition, each group being preceded by a general discussion. These general articles have been revised when necessary to bring them up to date. Such revisions have been made this year in the general articles Barbital and Barbital Compounds, Calcium Compounds, Cinchophen and Cinchophen Compounds, Digestive Enzymes, Cod Liver Oil and Cod Liver Oil Preparations, Ovary, Pituitary Gland, Radium and Radium Salts, and Serums and Vaccines. An article on Viosterol, the name adopted by the Council for irradiated ergosterol, has been added, under which are listed the preparations of this new therapeutic agent which the Council has accepted.

The statements concerning the actions, uses or dosage of the following have been revised: Antidysenteric Serum, Antimeningococcus Serum, Barbital, Bacillus Acidophilus Culture

(B. A. Culture) (B. B. Culture Laboratory, Inc.), Benzyl Alcohol, Bothrops Antitoxin, Concentrated Culture of Bacillus Acidophilus-P. D. L., Crotalus Antitoxin, Digitos, Diphtheria Toxin-Antitoxin Mixture, Erysipelas Antitoxin, Iodipin, Izal, Lipiodol-Lafay, Phenobarbital, Phentetiothalein Sodium, and Tetiothalein Sodium. The statement of composition, of standard of purity, identity or strength, or of physical qualities has been revised in the cases of the following: Albumen Milk-Hoos, Bismuth Salicylate in Oil-P. D. & Co., Bacillus Acidophilus Culture (B. A. Culture) (B. B. Culture Laboratory, Inc.), Erysipelas Streptococcus Antitoxin (Concentrated)-Mulford, Elixir of Luminal, Mercurosal, Metaphen, Oscodal, Pollen Extracts-Swan-Myers, Tablets Tutocain (with Epinephrine), and Typhoid-Paratyphoid Prophylactic (Cutter).

Solutions referred to in the descriptions of qualitative and quantitative tests are, unless otherwise stated, of the strength described in the U. S. Pharmacopeia.

In the description of an article, the statement, "No. U. S. patent," means that the manufacturer of that article has transmitted to the Council no claim of patent protection for it; and the statement, "No U. S. trademark," signifies that the manufacturer has claimed no trademark registration in connection with the name of the article.

During the year 1930, descriptions of such other medicinal substances as are accepted by the Council for New and Nonofficial Remedies will be published from time to time in *The Journal A. M. A.,* and will be reprinted in the form of supplements, which will be sent to those who purchase this book.

W. A. PUCKNER, Secretary.

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LIST OF CONSULTANTS

During the year the Council has had the assistance and advice of the following, consulted for their special knowledge and training in certain fields:

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OFFICIAL RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY

Introduction

Object of the Rules.—The following rules have been adopted by the Council primarily with the object of protecting the medical profession and the public against fraud, undesirable secrecy and objectionable advertising in connection with proprietary medicinal articles.

Contents of N. N. R.—The book New and Nonofficial Remedies contains a description of proprietary articles which have been accepted as conforming to the rules of the Council; of such simple nonproprietary and nonofficial substances as seem of sufficient importance to warrant their inclusion; and of simple pharmaceutical preparations, the inclusion of which is believed to give useful information to physicians.

Attitude on Mixtures.—For admission to N. N. R., proprietary pharmaceutical mixtures must comply with the rules; and, to determine such compliance, they will be investigated by the Council. The Council, however, endorses the principle that prescriptions should be written on the basis of the therapeutic effects of the individual ingredients. For this reason, it includes in this book only those mixtures that present some real advantage.

Rules Governing the Admission of Proprietary Articles to the Book New and Nonofficial Remedies

Definition of Proprietary Articles.—The term "proprietary article," in this place, shall mean any chemical, drug or similar preparation used in the treatment of diseases, if such article is protected against free competition, as to name, product, composition or process of manufacture by secrecy, patent, copyright, or by any other means.

Rule 1.—Composition.—No article will be accepted for inclusion in the book New and Nonofficial Remedies or retained therein unless its composition is published. For simple substances, the scientific name and the chemical formula, rational or structural, if known, should be supplied. For mixtures, the amount of each active medicinal ingredient in a given quantity of the article must be stated. The general composition of the vehicle, its alcoholic percentage, and the identity of the preservatives must be furnished.

Rule 2.—Identification.—No article will be accepted or retained unless suitable tests for determining its composition are furnished to the Council. In the case of chemical compounds, these shall consist of tests for identity and purity. In the case of mixtures, description of methods for determining the amount and strength of the potent ingredients shall be furnished, if practicable.

Rule 3.—Direct Advertising.—No article that is advertised to the public will be accepted or retained; but this rule shall not apply to (*a*) disinfectants, germicides and antiseptics, provided the advertising is limited to conservative recommendations for their use as prophylactic applications to superficial cuts and abrasions of the skin and to the mucous surfaces of the mouth, pharynx and nose (but not to those of the eye, and the gastro-intestinal and genito-urinary tracts) and provided they are not advertised as curative agents (see comments to Rule 3): (*b*) liquid petrolatum and simple preparations of liquid petrolatum, agar and simple preparations of agar, and similar preparations which act because of their bulk, provided that such lay advertising carries a warning that agar and similar preparations may be harmful in colitis; (*c*) other prophylactic agents about which the public should be informed which would not lead to harmful self-medication provided (1) that they are not advertised as curative agents and provided (2) that the advertising to the public does not go beyond that passed by the Council for physicians (Rule 6); and (*d*) medicinal food preparations, except when advertised as curative agents.

Rule 4.—INDIRECT ADVERTISING.—No article will be accepted or retained if the label, package or circular accompanying the package contains the names of diseases in the treatment of which the article is said to be indicated. The therapeutic indications and properties may be stated, provided such statements do not suggest self-medication. Dosage may be indicated. (This rule shall not apply to remedies with which self-medication is altogether improbable, to vaccines and antitoxins, or to directions for administering or applying remedies when similar immediate, heroic treatment is indicated.)

Rule 5.—FALSE CLAIMS AS TO ORIGIN.—No article will be accepted or retained concerning which the manufacturer or his agents make false or misleading statements as to source, raw material from which made, or method of collection or preparation.

Rule 6.—UNWARRANTED THERAPEUTIC CLAIMS.—No article will be accepted or retained concerning which the manufacturer or his agents make unwarranted, exaggerated or misleading statements as to the therapeutic value.

Rule 7.—POISONOUS SUBSTANCES.—The principal label on an article containing "poisonous" or "potent" substances must state plainly the amount of each of such ingredients in a given quantity of the product.

Rule 8.—OBJECTIONABLE NAMES.—Proprietary names for medicinal articles will be recognized only when the Council shall deem the use of such exclusive names to be in the interest of public welfare. Names which are misleading or which suggest diseases, pathologic conditions or therapeutic indications will not be recognized (the provision against therapeutically suggestive names does not apply to serums, vaccines and antitoxins). In the case of pharmaceutical preparations or mixtures, the name must be so framed as to indicate clearly the most potent ingredients.

Rule 9.—PATENTED PRODUCTS AND PROTECTED NAMES.—If the article is patented—either process or product, or both—the number of such patent or patents must be furnished to the Council. Furthermore, if the name of an article is registered, or the label copyrighted, the registration (trademark) number and a copy of the protected label should be furnished the Council. In case of registration in foreign countries, the name under which the article is registered should be supplied.

Rule 10.—UNSCIENTIFIC AND USELESS ARTICLES.—No article will be accepted or retained which, because of its unscientific composition, is useless or inimical to the best interests of the public or of the medical profession.

Rule 11.—POLICIES OF FIRMS DETRIMENTAL TO RATIONAL THERAPEUTICS.—The Council will not accept or retain, if already accepted, the articles of a firm if in the opinion of the Council the policies of such a firm are clearly detrimental to the welfare of the public and to medicine.

EXPLANATORY COMMENTS ON THE RULES

PURPOSE AND METHODS OF THE COUNCIL.—The Council on Pharmacy and Chemistry was established in 1905 by the American Medical Association, primarily for the purpose of gathering and disseminating such information as will protect the medical profession in the prescribing of proprietary medicinal articles. In pursuance of this object, the Council examines the articles on the market as to their compliance with definite rules designed to prevent fraud, undesirable secrecy and the abuses which arise from advertising directly or indirectly to the laity. Such articles as appear to conform to the rules are accepted, and their essential features are described in the annual publication of the Council, New and Nonofficial Remedies, if they come within the scope of this book.

Submitted Evidence.—These descriptions are based in part on investigations made by, or under, the direction of the Council, but in part also on evidence or information supplied by the manufacturer or his agents. Such interested statements are examined critically, and are admitted only if they appear to be in conformity with the evidence. It is, however, manifestly impossible for the Council to investigate the composition of every complex pharmaceutical mixture, or to check thoroughly every therapeutic claim; it can give only an unbiased judgment on the available evidence. Criticisms and corrections of the descriptions which may aid in the revision of the matter will be appreciated.

Previous Noncompliance and Fraud.—The Council judges an article entirely by the facts in evidence at the time of its admission. Previous noncompliance with the rules (short of *intentional* fraud) does not prevent the favorable consideration of an article which is in accord with existing rules.

Reconsideration.—Infringements of the rules after acceptance of an article for New and Nonofficial Remedies, or the discovery that the Council's information was incorrect, will cause the acceptance to be reconsidered. An article is accepted for New and Nonofficial Remedies, and will continue to be included in the book, with the understanding that serious violations of the rules, after acceptance, will be followed by the omission of the article and publication of the reasons for such omission.

Acceptance Not an Indorsement.—The Council desires physicians to understand that the admission of an article does not imply a recommendation. Acceptance simply means that no conflict with the rules has been found by the Council.

Duration of Acceptance.—Unless otherwise determined at the time of acceptance, articles admitted to New and Nonofficial Remedies will be retained for a period of three years, provided that during that period they comply with the rules and regulations which were in force at the time of their acceptance. New evidence indicating that compliance with the rules no longer exists, for instance, with regard to unwarranted therapeutic claims, will be considered the basis for reconsidering the acceptance before the end of a period of three years. At the end of this period, all articles will be carefully reexamined for compliance with existing rules. Particular weight will be given to the question as to whether recent evidence has substantiated claims as to the therapeutic value of any preparation, this evidence to consist partly of recent statements in the literature and partly of the general esteem in which the preparation is held by clinical consultants of the Council. The reacceptance of articles after such reexamination shall be for three years unless a shorter period is specified.

Any amendments to the rules, by specific requirements or by interpretation, which may be made after the acceptance of an article, shall not apply to such article until the period of acceptance has elapsed. At the end of this period the article, if it is not eligible under the amended rules, will be omitted.

THE SCOPE OF NEW AND NONOFFICIAL REMEDIES.—To aid physicians and manufacturers in deciding which articles come within the scope of this book, or, in other words, to enable physicians to recognize whether an article which is not described in New and Nonofficial Remedies has not been included because it has been held not to come within the scope of N. N. R. or because it has been rejected, the Council furnishes the following more detailed definitions:

Official Articles.—Articles official in the U. S. P. or N. F. are exempted from consideration by the Council if they are marketed under the official name or a name which makes their official status evident, and if no unestablished therapeutic claims are made for them.

These do not require consideration by the Council, since standards for them are provided in these books, and enforced under the provisions of the federal Food and Drugs Act, except that they may be mentioned for information.

If a U. S. P. or N. F. product is offered for sale under a name which does not make its official status evident, or if the proprietors or their agents advance claims that the product possesses therapeutic properties other than those commonly accredited to it, it becomes subject to consideration by the Council.

Simple preparations or mixtures of official articles may be considered to have the status of official articles if they are marketed under descriptive, nonproprietary names and if unestablished claims are not made for them. At the request of the distributors of such products the Council will determine whether they meet these provisions, and if they are found not to require inclusion in N. N. R. they will be included in a list of "exempted" articles.

Modifications of U. S. P. and N. F. Products.—A Pharmacopeial or National Formulary product which is marketed under the official title or synonym, but with well-founded claims that its purity, permanence, palatability or other physical properties excel the official standard, may, if no extraordinary therapeutic properties are asserted, be considered as an official article and held not to be within the scope of New and Nonofficial Remedies.

When such products are marketed under the claim that they possess therapeutic properties other than those commonly accredited to the U. S. P. or N. F. products of which they are modifications, they become subject to the consideration of the Council.

The burden of proof in establishing claims for therapeutic properties of products considered by the Council shall lie with the proprietor or, in the case of a foreign-made product, with the agent who markets the product in the United States.

Substances Described in New and Nonofficial Remedies.—In the book will be described simple proprietary substances and their preparations; proprietary mixtures if they have originality or other important qualities which, in the judgment of the Council, entitle them to such place; important nonproprietary nonofficial articles; and simple pharmaceutical preparations, the inclusion of which is believed to give useful information to the physician.

Proprietary Mixtures.—A mixture will be considered as proprietary, and therefore requiring consideration by the Council for admission to the book, if it contains any proprietary articles; if it is marketed under a name which is in any way protected, or if its manufacturer claims for it any unusual therapeutic qualities.

Diagnostic Reagents.—Reagents and other drug preparations which are not used in or on the human body, and protein preparations used for diagnosis only shall not be considered for inclusion in N. N. R. At the request of the distributor the Council will determine the status of such products individually, and if the product is found not to require inclusion in N. N. R. it will be included in a list of "exempted" articles.

Medicinal Foods.—The Council examines food preparations which are advertised to the medical profession (except natural foods in their natural form) when such consideration is requested by the proprietors or if a request for such consideration is received from the publication considering the acceptance of such advertising. Foods which are found to have therapeutic properties and are considered of sufficient originality will be admitted to N. N. R. if they otherwise comply with the rules. Medicinal foods which are not of sufficient originality but are marketed under descriptive nonproprietary names and with well founded claims will be reported on favorably and placed on the list of "exempted" medicinal articles but not described in N. N. R.

Nonmedicinal Foods.—The Council has established a Committee on Foods to examine nonmedicinal foods for which health claims are made. Such foods, if they meet the requirements of the rules which have been adopted, will be accepted for inclusion in Accepted Foods, a publication distinct from New and Nonofficial Remedies, sponsored by the Committee on Foods.

Articles Not Considered.—Mineral waters (natural), at the present time, shall not be considered by the Council. Mechanical appliances, at the present time, shall not be considered by the Council.

Suffix N. N. R.—When nonproprietary articles included in New and Nonofficial Remedies are prescribed, the Council recommends that they be indicated by the abbreviation "N. N. R.," thus insuring to the prescriber the quality of these articles laid down in the book.

Rule 1.—COMPOSITION.—*Secrecy Objectionable.*—It is not only the right but also the duty of the physician to know the essential composition of what he prescribes; the Council cannot compromise on this proposition.

Statement of Composition.—In the case of a definite chemical substance, a descriptive name, satisfactory to the Council, must appear on the label and in the advertising. For mixtures, the label and advertising must contain a statement of the amount of each potent or important ingredient in a given quantity of the mixture.

Vehicles and Preservatives.—In the case of mixtures, not only the potent ingredient, but also the general character of the vehicle, the presence of alcohol, and the identity of preservatives, or of any other substance, whether added or present as an impurity, must be stated if these can under any circustances affect the therapeutic action of the article. This, as a rule, does not mean the publication of trade secrets, such as flavors or the details of the working formula.

Trade Secrets.—Furthermore, trade secrets will not be received as confidential by the Council, since it accepts information only with the distinct understanding that this may be freely published, at its discretion.

Inspection of Factories.—The Council does not accept invitations to inspect factories; its concern is with the finished products.

On the other hand, the Council requires that the information be complete and accurate as to medicinal ingredients.

Nonofficial Constituents.—Nonofficial constituents of proprietary mixtures must be presented by the manufacturer in the regular way and must be acted on by the Council before the preparations containing them can be accepted.

Fraud.—When it appears that a manufacturer has made a *deliberately* false statement concerning a product, he is asked to furnish an explanation; and if this is not satisfactory, the product will not be accepted, even if the false statement is subsequently corrected or omitted.

Testimonials.—The foregoing paragraph applies not only to statements made to the Council, but also to statements furnished to physicians by the manufacturer or his agents, even when these statements are in the guise of testimonials.

Rule 2.—IDENTIFICATION.—In order to avoid errors in the case of chemical compounds, and to guard against adulterations, lack of potency or strength and the mistaking of one chemical for another, it is necessary to have at hand suitable tests.

Tests, etc.—If these facts have appeared in the literature, or in standard textbooks, reference to them will be sufficient; but with new chemicals, especially synthetics, the manufacturer or his representatives will be required to supply such tests for publication as will assure an intelligent opinion of these products.

Physiologic Standardization.—In cases in which chemical methods of identification are unknown or unreliable, physiologic standardization should be employed. The Council considers the phrase "physiologically standardized" or "assayed" as misleading unless the standard and method are published in sufficient detail to permit of their control by independent investigators.

It is evident that when no standard is published, it is impossible to know whether the quality is high or low, and the conscientious manufacturer who sets for himself a high standard is placed on a level with the dishonest or careless one who adopts a low standard. Again, if the process of standardization is not published, it is impossible to learn, without actual trial, the relative value of one preparation as compared with that of another manufacturer or to confirm or disprove the statements of the manufacturer as to the quality of his product.

Standardization of Disinfectants and Germicides.—No disinfectant or germicide of the phenol type will be accepted for N. N. R. whose phenol coefficient, determined with *B. typhosus* according to the method of the Hygienic Laboratory, U. S. P. H. S., is not stated on the label of the preparation.

Rule 3.—DIRECT ADVERTISING. —*Lay Advertising.* — The impossibility of controlling the irresponsible claims which are usually made in advertisements to the public, the well-known dangers of suggesting by descriptions of symptoms to the minds of the people that they are suffering from the many diseases described, the dangers of the unconscious and innocent formation of a drug habit, and the evils of harmful self-medication, including the dangers of the spread of many infections and contagious diseases when hidden from the physician, and similar well-known considerations, are the reasons for discouraging, in the interest, and for the safety, of the public, this reprehensible form of exploitation. Advertising in medical journals, etc., distributed solely to physicians, does not come within the scope of this rule.

Exceptions.—In the case of subjects on which the public should be instructed, as the use of certain disinfectants, germicides, antiseptics, certain laxatives and foods, advertisements to the public, if not in objectionable forms, are considered admissible. In no case shall such advertisements include recommendations for use as curative agents, nor shall the names of any diseases appear on or in the trade package. If the preparation is sufficiently toxic to require caution in its use to prevent poisoning, this fact shall be stated on the label. On account of the deplorable results which would follow any abuse of this privilege the conscientious cooperation of manufacturers and their agents in adhering strictly to the limitations laid down is asked; and for the same reason the acceptance of an article which is so advertised as to infringe on these limitations in any essential way (as by naming diseases or by making false and exaggerated claims) shall be summarily rescinded, and the reasons for such action may be published without notice to manufacturer or agent. A disinfectant, germicide or antiseptic will be accepted for description in New and Nonofficial Remedies, and an article of this class which has already been accepted will continue to be included in New and Nonofficial Remedies only on the explicit understanding by the manufacturer and agent that such infringements of the rule will be followed by deletion of the article and by publication of the facts as described.

Advertisements in Foreign Countries.—The Council deals primarily, in the interest of the public and of the medical profession, with articles proposed for admission to New and Nonofficial Remedies, and, in determining the status of any article, must take into consideration any statements made regarding it or any method of advertising it employed by the manufacturer or his authorized agents or representatives, whether in this country or abroad. The Council will not regard as within its scope, however, questions concerning the marketing of articles (except the matter of direct advertising to the laity and unwarranted claims or misrepresentations) outside the United States.

Rule 4.—INDIRECT ADVERTISING.—It should be remembered that the sole intent of this rule is to protect the physician, so that in prescribing a proprietary medicine he shall not unconsciously advertise proprietary preparations. The rule imposes no restriction on the legitimate methods of bringing a remedy to the attention of the profession, such as advertising in medical journals, circulars and other printed matter distributed solely to physicians. The rule applies only to the package as it may reach the patient.

Naming Diseases on Label.—The naming of diseases on the label or package is not necessary, as is shown by the very large number of proprietary products which have been successfully introduced without resorting to this expedient. This method of popularizing a proprietary remedy with the laity is most objectionable, and should not be tolerated in any form.

Therapeutic Indications—In general, therapeutic indications should be omitted from the label and package. The Council will not insist on this point, however, when such indications are so given as not to promote self-medication, particularly in diseases which require expert diagnosis and supervision.

Permanently Affixed Names.—It will be considered an infringement of the rule if an article is marketed in bottles which have the name of the article blown into the glass, or if otherwise the name or initials or other distinctive mark of the article is permanently stamped on the container, on the article itself, or is on the stoppers or seals. Articles which are marketed in any of these ways are not accepted for New and Nonofficial Remedies. Readily removable labels are not objectionable nor is the permanent affixing of the firm's initials or name to the trade package if such initials or name is not suggestive of the article.

Use of Articles for Advertising.—The Council does not countenance the use of an accepted article for advertising other articles which have not been accepted by the Council; this applies to circular matter dealing with such accepted articles whether included with the trade packages or otherwise, but does not apply to pricelists, catalogues, and other general advertising. Nor will the Council accept an article or continue the acceptance of an article, if the same article or an essentially similar one is marketed by the same firm under another name which has not been recognized. When, in the opinion of the Council, a firm secures the acceptance of one or more articles and employs the acceptance in a way that promotes the exploitation of articles that are opposed to the principles of the rules of the Council, the preparations of the firm will be dismissed summarily and no preparations of that firm will be accepted by the Council.

Rule 5.—FALSE CLAIMS AS TO ORIGIN.—No false or misleading statement in regard to an article can be permitted concerning the source or material from which it is made, or the persons by whom it is made. Some glaring frauds of this nature have been perpetrated in the past, and this rule is intended to prevent such imposition.

Rule 6.—UNWARRANTED THERAPEUTIC CLAIMS.—This rule insists that the claims of manufacturers or agents concerning the therapeutic properties of their products must be compatible with demonstrable facts. Manufacturers will be held responsible for all statements made or quoted in their advertising "literature" regarding their products. Recognizing the existence of honest differences of opinion on many therapeutic questions, the Council desires to be liberal in the application of this rule. It is natural that a manufacturer should be partial toward his own product, and a moderate degree of emphasis in advertising may not be objectionable. The Council, however, will not admit claims which are neither in harmony with already accepted facts nor supported by acceptable evidence. In doubtful cases the Council considers these questions with the advice and cooperation of its staff of clinical consultants.

Therapeutic claims that do not exceed the statements in the current New and Nonofficial Remedies will not be challenged as a rule; but if the Council finds reason to doubt the validity of any description in New and Nonofficial Remedies, it may require the manufacturer to submit further evidence if he desires to continue such claims. Since the claims of the manufacturers are judged largely by their advertising, noncompliance of the manufacturers with the Council's request for copies of the current advertising may be sufficient ground for the rejection of an article, unless in individual cases the Council deems such submission unnecessary.

Clinical Evidence.—To be acceptable, the clinical evidence must offer objective data with such citation of authority as will enable the Council to confirm the facts and establish the scientific value of the conclusions drawn. The amount and character of the evidence which is required depends on the inherent probability of the claims; no evidence is needed for a self-evident claim; very strong evidence is needed when the claim is contrary to the accepted data of science. The acceptability of evidence is determined mainly by its quality. The mere multiplication of inaccurate observations does not render them accurate. The evidence must be furnished in sufficient detail to permit judgment as to the care with which it was gathered and the legitimacy of the deductions. Comparative trials facilitate and are often necessary for such judgment. Observations that are not described with sufficient detail to permit verification, are subject to suspicion. The credibility of the data and the justification of the deductions is influenced by the reputation and experience of the investigators, as to disinterestedness, technical ability, and critical sense. Anonymous communications and observations gathered without adequate facilities are usually worthless as evidence.

Rule 7.—POISONOUS SUBSTANCES.—For the information of the pharmacist or dispenser, and to enable him to safeguard the interests of the patient and the physician, all articles containing such potent agents as the poisonous alkaloids and other organic substances and the salts of some of the metals should have the exact amount of these ingredients which is contained in the average adult dose stated on the label.

Rule 8.—OBJECTIONABLE NAMES.—Many of the abuses connected with proprietary medicines arise from "coined" proprietary trade names. Such names will not be recognized by the Council unless in particular instances the Council shall deem their use to be in the interest of public welfare. In every such exception the burden of proof, both for establishing and for continuing the exception, lies with those who market the product.

Proprietary ("Trade") Names; When Permitted.—In consideration of the benefits which may come from the discovery of a therapeutic agent, the Council concedes to the person or firm which, by right of discovery, controls such a product the right to name it. The Council will offer no opposition to an arbitrary name for such a new product, provided it is not misleading, therapeutically suggestive, or otherwise subversive of scientific pharmacy and therapeutics. If the discovery that a previously known substance has therapeutic value is deemed of sufficient importance, the Council may recognize a name for such a substance if the name is applied by the person who makes the discovery; or, with the consent of the discoverer or in the absence of any protest on his part, the Council may recognize a name applied by the firm which first makes such a product available to physicians. Under these conditions the Council may also recognize proprietary names when new uses or actions of exceptional novelty and importance are discovered for substances previously used in medicine, but which had become practically obsolete. In the interest of rational drug therapy, the Council recommends that trade names be coined so as to indicate the potent element or constituent.

When the proprietary or trade name for an article is considered insufficiently descriptive of its chemical composition or pharmaceutical character, the Council may require as a condition for the acceptance of such articles that a descriptive scientific name satisfactory to the Council appear on the labels, circulars and advertisements for such an article. For all definite chemical substances it is required that the scientific name be given prominence on the labels, in circulars and advertisements.

Proprietary Names for Unoriginal Articles.—Proprietary names will not be recognized for articles which are included in the U. S. Pharmacopeia or National Formulary or for unessential modifications of such articles. Neither will proprietary names be recognized for substances or mixtures which are described in medical or pharmaceutical publications, except in connection with fundamentally important discoveries relating to articles whose use had become practically obsolete.

In the marketing of unoriginal articles, the legitimate interests of the producer are fully served by identifying such products by appending the name or initials of the manufacturer or agent, or by the use of a general brand mark. No objection will be made by the Council to the use of such brand marks, provided that in no case shall such mark be used as a designation for an individual article.

For any product which, by reason of the absence or lapse of patent rights or for other reasons, is open to manufacture by more than one firm, the Council reserves the right to select a common name and to provide standards of identity, purity and strength, and then will accept such article only if it is marketed under the title adopted as the N. N. R. name or the name under which such article was introduced (to which may be appended the firm's identifying mark).

When an article which has been accepted for New and Nonofficial Remedies is admitted to the U. S. Pharmacopeia or National Formulary, it will be omitted from New and Nonofficial Remedies one year after such standardization if the name of such article is used in these standards either as the main title for the product or as a synonym. If the name under which the article is described in New and Nonofficial Remedies is not used in these books of standards, the proprietary preparation will be retained provided the official name is given prominence on the labels and in the circulars and advertisements of such article.

When the Council adopts a common name for an article that has been admitted under another name, it will be continued under the older name only on condition that the Council name be given prominence on the label and in the circulars and advertisements for such article.

Pharmaceutical Preparations and Mixtures.—These, with rare exceptions, are not original in composition and should not be endowed with uninforming names. It is important that they be so named as to remind the prescriber constantly of their potent ingredients. When, in the rare exception, a pharmaceutical preparation or mixture is accepted with a coined name on the ground of originality because it presents a distinct improvement over available preparations, only the first preparation of this kind which is placed on the market shall be recognized under a coined name (which, however, must clearly indicate the potent constituent of the preparation). The Council may also recognize coined names for pharmaceutical preparations or mixtures that were in actual use before the establishment of the Council and that have been used continuously since that time, and names for mixtures that were named under the reasonably justified bona fide belief that they were chemical compounds, provided that such coined names indicate the potent ingredient or ingredients of the preparation, are not misleading, and do not suggest diseases, pathological conditions, or therapeutic indications.

Therapeutically Suggestive Names.—Names which carry the suggestion of a therapeutic indication, pathologic condition, disease, or organism causing a disease shall be considered therapeutically suggestive. Articles bearing such names will not be accepted for New and Nonofficial Remedies, first, because they are likely to lead physicians into prescribing names instead of remedies, and second, because they tend to encourage unwarranted self-medication by the laity. Even if the name is at first apparently meaningless to the public, its meaning will soon be understood because patients soon learn the technical names applied to their diseases and symptoms.

The prohibition against therapeutically suggestive names is not applied to serums, vaccines and antitoxins, because the accepted nomenclature of the specific organisms used in their preparation makes this unavoidable and because self-medication with them is improbable.

Rule 9.—PATENTS, TRADEMARKS, COPYRIGHTS, ETC. — This information is important as a means of determining the legal status of medicinal articles and as an aid to their ready recognition in current publications.

Rule 10.—UNSCIENTIFIC AND USELESS ARTICLES.—The use of articles which are unessential modifications of official or established nonproprietary articles is unscientific and serves no useful purpose. The Council will not accept products which are scientifically unsound and which, therefore, must be considered useless or inimical to the best interest of the medical profession and the public. This class includes compounds or mixtures containing an excessive number of active ingredients; those compounds or mixtures the components of which are of no probable assistance to one another, and those articles which are of no therapeutic value.

UNESSENTIAL MODIFICATIONS OF OFFICIAL SUBSTANCES.—*Imitations.*—The subterfuge of obtaining proprietary rights over an official or established nonproprietary product, by introducing unessential modifications, also tends to confusion and abuses, and such articles will not be admitted by the Council. Essential and important modifications, however, will receive recognition. (The Council interprets the term "established nonproprietary product" as applying to a preparation of any formula which has been published through any recognized or reasonably accessible channel of publication, prior to its appropriation or modification by a manufacturer.) Duplicates of biologic products accepted under the names of the manufacturers will not be accepted under the names of the distributors.

Rule 11.—POLICIES OF FIRMS DETRIMENTAL TO RATIONAL THERAPEUTICS.—The evidence on which the Council may refuse recognition to the products of a firm shall be: (1) the fact that but a small proportion of the firm's proprietary products are acceptable for New and Nonofficial Remedies; or (2) that a large proportion of the business of the firm is in products that are in conflict with the rules of the Council; or (3) that physicians who reply to the firm's advertisements of accepted products are supplied with advertising which features the use of products that are in conflict with the Rules of the Council; or (4) that the firm makes claims that are seriously misleading; and especially if these claims tend to promote the use of products in any manner that would seriously endanger public health.

NEW AND NONOFFICIAL REMEDIES

AGAR AND AGAR PREPARATIONS

AGAR.—Agar-Agar.—For description see the U. S. Pharmacopeia under Agar.

Agar-Agar Powder-Merck.
Prepared by Merck & Co., Inc., Rahway, N. J.

Agar-Agar Shreds-Merck.
Prepared by Merck & Co., Inc., Rahway, N. J.

PHENOLPHTHALEIN-AGAR.—Agar impregnated with phenolphthalein, 100 Gm. containing 3 Gm. of phenolphthalein.

Actions and Uses.—Phenolphthalein-agar is claimed to have the properties of agar augmented by the action of phenolphthalein.

Dosage.—1 Gm. (15 grains), twice daily, after breakfast and supper, increased or diminished according to requirements.

Manufactured by The Reinschild Chemical Company, New York. U. S. patent 943,163 (Dec. 14, 1909, expired). No U. S. trademark.

Phenolphthalein-agar is prepared by impregnating 1,000 Gm. of agar with a solution obtained by dissolving 30 Gm. of phenolphthalein in a mixture of 2,000 cc. of water and 700 cc. of alcohol and slowly drying the impregnated agar.

ALLERGIC PROTEIN PREPARATIONS

Allergic protein preparations are extracts prepared from the proteins of various substances believed to be responsible for sensitization of patients suffering from various affections. These preparations are used for diagnosis, prophylaxis or desensitization of conditions due to hypersensitiveness (allergy). They are made from the proteins of pollens believed to be the cause of hay-fever; from the proteins obtained from the hair or epidermis of animals or the feathers of fowls; from the purified proteins of various biologically reactive foods; from the proteins extracted from bacterial cells, and from proteins derived from other sources and believed to be responsible for cases of allergy. Only proteins from a single source are accepted—that is, from a single species if an extract from the pollen of plants, hair or epidermis of animals, or the feathers of fowls is employed; from a single strain of bacteria, or from a single food.

Practically all observers agree that the majority of cases of hay-fever may be traced to the pollens from the following sources: timothy, which is the cause of spring hay-fever in the East; certain grasses which are the causes of spring hay-fever in the Middle West; and ragweed, which is the common cause of autumn hay-fever throughout the Middle West and the East. For practical purposes, in the East, at least 90 per cent of the cases can be treated by two extracts alone. In the other cases, the sensitiveness of the patient must be determined by a series of tests with pollens indigenous to the locality in which the patient lives. It is often more convenient and satisfactory to prepare extemporaneously the pollen or the epidermal extracts to meet the needs of the individual case.

Since liquid pollen and epidermal extracts deteriorate with age, it is necessary, in order to insure their potency, that they be used before the expiration of a given time (determined by the regulations of the U. S. Treasury Department). Pollen extracts containing at least 50 per cent of glycerin should be used within two years of the date of their preparation, while those containing less glycerin or which are supplied in aqueous saline solutions should be used within one year of the date of preparation. Alcoholic epidermal extracts should be used within two years of the date of their preparation, while aqueous extracts should be employed within one year of the date of their preparation. All pollen and epidermal extract preparations should be kept at low temperature. Attention is called to the fact that, even under these circumstances, extracts in high dilutions are more liable to deterioration than more concentrated solutions. To insure sterility, the Council requires that liquid extracts intended for purposes other than diagnostic shall be put up in such a way as to avoid contamination and that their sale shall be authorized by the U. S. Treasury Department under the law governing the sale of biologic products.

Actions and Uses.—Pollen extract is employed for the diagnosis, prophylaxis, or relief of a common type of hay-fever—pollinosis. A pollen extract prepared from the pollen of one plant is not intended for use in pollinosis caused by the pollen from other plants, though persons suffering from hay-fever frequently react to the pollen of more than one species.

The patient's susceptibility may be tested by rubbing a small quantity of the pollen extract into a scratch of the skin; if the patient is sensitive to that particular pollen, an urticarial wheal results. To avoid systemic disturbance, it is recommended that no therapeutic injections be made until the reaction from this cutaneous test has subsided completely. When treatment with pollen extract is carefully and systematically pursued, it gives complete relief from symptoms in a few instances, considerable relief from symptoms in a large proportion of cases, and fails to give any relief in a small number of cases. The immunity from symptoms resulting from treatment is apparently not permanent, and in most cases does not last longer than a year.

Epidermic protein extracts are employed for the diagnosis and relief of asthma or perennial rhinitis. The patient's susceptibility may be tested in the same manner as that employed with the pollen extracts. Therapeutic injections have been employed in an attempt to relieve the paroxysms of asthma, but the results of treatment have not seemed so satisfactory or so lasting as those obtained from the use of pollen extracts in hay-fever.

The food protein extracts are used in cases in which persons show a peculiar hypersentitiveness toward certain articles of the dietary. Their purpose is twofold: to identify the food which produces the untoward symptoms, and, to a lesser extent, to immunize the patient by their proper application against the ill effect of this food.

The bacterial protein extracts are used cutaneously for the diagnosis of anaphylaxis to the metabolic products from specific bacteria. Their utility is debatable.

In order that the number of skin tests to determine sensitiveness to proteins may be reduced, it has been proposed to employ mixtures of protein preparations, and if sensitiveness to a given mixture is found, then to make tests with the individual proteins contained in this mixture. There is the objection to this procedure that with patients who react very slightly to one member of a mixture, the dilution which has occurred on account of the presence of other proteins may render a reaction negative. On the other hand, if a patient is highly sensitive to all the proteins of a mixture, cutaneous reactions may give rise to systemic disturbances.

Dosage.—It is regarded as important that the individual dosage be determined by testing each patient's susceptibility to the specific protein extract, as sensitiveness varies greatly and an overdose may cause disagreeable or alarming symptoms or even death. A method used for such test is to make a series of scratches on the patient's skin (it is important that these should be made at some distance from the scratches of the first test) and to apply to these scratches 25 per cent, 10 per cent, 1 per cent, or even weaker dilutions of the protein extract. From 2 to 5 drops of the dilution which fails to produce a definite skin reaction may be injected subcutaneously as the first dose. Injections, increased by a few drops at first, and later by the use of a stronger dilution, may then be given at intervals of a few days or a week.

Owing to the relative insolubility of most of the food protein preparations and the difficulty of preparing them in sterile form, they cannot with safety be injected intradermally, and, therefore, the tests for hypersensitiveness must be made by the cutaneous or scarification method. The intensity of the reaction will depend somewhat on the concentration of the protein solution. No systemic effect should be produced.

When the identity of the particular food protein causing the symptoms is thus established, it has been found that the patient may be desensitized by the administration of gradually increasing amounts of food containing the offending protein or of the isolated food protein itself. If the isolated food proteins are used, they are best administered, mixed with the ordinary foods. The dose at first should not exceed from 0.005 Gm. to 0.01 Gm., and, in highly sensitive individuals and children, it is best to start with a dose not larger than from 0.0005 Gm. to 0.001 Gm. In some cases, the skin reaction serves as an indication of the effect being produced by the dosage employed. Occasionally, the skin reaction decreases in intensity or disappears as the dosage is increased, but, in most instances, the skin reaction persists even though the patient is able to withstand fair amounts of the food to which he had previously been sensitive. The efficiency of the treatment can be judged by the patient's ability to ingest, without ill effects, large quantities of the food protein which previously had produced the untoward symptoms.

Simple Protein Preparations

CONCENTRATED POLLEN EXTRACTS-SWAN-MYERS.—Liquids obtained by extracting the dried pollen of plants with a liquid consisting of 67 per cent of glycerin and 33 per cent of a buffered salt solution.

Actions and Uses.—See preceding article, Allergic Protein Preparations.

Dosage.—See preceding article, Allergic Protein Preparations.

Concentrated pollen extracts-Swan-Myers are marketed in 5 cc. vials.

Manufactured by Swan-Myers Company, Indianapolis, Ind. No U. S patent or trademark.

Annual Sage Concentrated Pollen Extract-Swan-Myers; Arizona Ash Concentrated Pollen Extract-Swan-Myers; Ash Concentrated Pollen Extract-Swan-Myers; Bermuda Grass Concentrated Pollen Extract-Swan-Myers; Black Walnut Concentrated Pollen Extract-Swan-Myers; Biennial Sage Concentrated Pollen Extract-Swan-Myers; Blue Grass Concentrated Pollen Extract-Swan-Myers; Box Elder Concentrated Pollen Extract-Swan-Myers; Burweed Marsh Elder Concentrated Pollen Extract-Swan-Myers; Canada Blue Grass Concentrated Pollen Extract-Swan-Myers; Cocklebur Concentrated Pollen Extract-Swan-Myers; Corn Concentrated Pollen Extract-Swan-Myers; Cosmos Concentrated Pollen Extract-Swan-Myers; Costal Sagebrush Concentrated Pollen Extract-Swan-Myers; Cottonwood Concentrated Pollen Extract-Swan-Myers; Crab Grass Concentrated Pollen Extract-Swan-Myers; Dandelion Concentrated Pollen Extract-Swan-Myers; English Plantain Concentrated Pollen Extract-Swan-Myers; Elm Concentrated Pollen Extract-Swan-Myers; False Ragweed Concentrated Pollen Extract-Swan-Myers; Giant Ragweed Concentrated Pollen Extract-Swan-Myers; Goldenrod Concentrated Pollen Ertract-Swan-Myers; Goose Grass Concentrated Pollen Extract-Swan-Myers; Hemp Concentrated Pollen Extract-Swan-Myers; Hickory Concentrated Pollen Extract-Swan-Myers; Johnson Grass Concentrated Pollen Extract-Swan-Myers; Lamb's Quarters Concentrated Pollen Extract-Swan-Myers; Marsh Elder Concentrated Pollen Extract-Swan-Myers; Mixed Ragweed (Ambrosia elatior and Ambrosia trifida) Concentrated Pollen Extract-Swan-Myers; Mountain Cedar Concentrated Pollen Extract-Swan-Myers; Mugwort Concentrated Pollen Extract-Swan-Myers; Oak Concentrated Pollen Extract-Swan-Myers; Orchard Grass Concentrated Pollen Extract-Swan-Myers; Ox-Eye Daisy Concentrated Pollen Extract-Swan-Myers; Palmer's Amaranth Concentrated Pollen Extract-Swan-Myers; Plantain Concentrated Pollen Extract-Swan-Myers; Prairie Sage Concentrated Pollen Extract-Swan-Myers; Quailbrush Concentrated Pollen Extract-Swan-Myers; Redroot Pigweed Concentrated Pollen Extract-Swan-Myers; Red Sorrel Concen-

trated Pollen Extract-Swan-Myers; Redtop Concentrated Pollen Extract-Swan-Myers; Russian Thistle Concentrated Pollen Extract-Swan-Myers; Sagebrush Concentrated Pollen Extract-Swan-Myers; Short Ragweed Concentrated Pollen Extract-Swan-Myers; Slender False Ragweed Concentrated Pollen Extract-Swan-Myers; Southern Ragweed Concentrated Pollen Extract-Swan-Myers; Spiny Amaranth Concentrated Pollen Extract-Swan-Myers; Sudan Grass Concentrated Pollen Extract-Swan-Myers; Sunflower Concentrated Pollen Extract-Swan-Myers; Sweet Vernal Grass Concentrated Pollen Extract-Swan-Myers; Sycamore Concentrated Pollen Extract-Swan-Myers; Timothy Concentrated Pollen Extract-Swan-Myers; Western Ragweed Concentrated Pollen Extract-Swan-Myers; Western Water Hemp Concentrated Pollen Extract-Swan-Myers; Yellow Dock Concentrated Pollen Extract-Swan-Myers; Yellow Fox-Tail Concentrated Pollen Extract-Swan-Myers.

Concentrated pollen extracts-Swan-Myers are prepared by grinding dried pollen with a menstruum composed of 67 per cent of glycerin and 33 per cent of a solution containing sodium chloride, 5 Gm., and sodium bicarbonate, 2.7 Gm., in distilled water, 1,000 cc. The extract is clarified by filtration and sterilized by passing the filtrate through Mandler filters. The finished liquid is a 3 per cent extract of the dried pollen, each cubic centimeter representing 0.03 Gm. dried pollen (30,000 units).

POLLEN ALLERGEN SOLUTIONS-SQUIBB.—Solutions containing the sodium chloride-soluble protein from the isolated pollen of various species of plants. Pollen Allergen Solutions-Squibb are intended for the prevention and treatment of hay fever.

Actions and Uses.—See preceding article, Allergic Protein Preparations.

Dosage.—See preceding article, Allergic Protein Preparations.

The following pollen allergen solutions-Squibb are marketed in 5 cc. vials for treatment (1 cc. = 0.025 mg. of pollen nitrogen):

Annual Salt Bush Pollen Allergen Solution-Squibb; Arizona Ash Pollen Allergen Solution-Squibb; Arizona Cottonwood Pollen Allergen Solution-Squibb; Arizona Walnut Pollen Allergen Solution-Squibb; Ash Pollen Allergen Solution-Squibb; Bermuda Grass Pollen Allergen Solution-Squibb; Black Mulberry Pollen Allergen Solution-Squibb; Black Walnut Pollen Allergen Solution-Squibb; Brome Grass Pollen Allergen Solution-Squibb; California Black Walnut Pollen Allergen Solution-Squibb; Careless Weed Pollen Allergen Solution-Squibb; Cedar Pollen Allergen Solution-Squibb; Cocklebur Pollen Allergen Solution-Squibb; Corn Pollen Allergen Solution-Squibb; Dandelion Pollen Allergen Solution-Squibb; Dark Leaved Mugwort Pollen Allergen Solution-Squibb; English Plantain Pollen Allergen Solution-Squibb; False Ragweed Pollen Allergen Solution-Squibb; Goldenrod Pollen Allergen Solution-Squibb; Hickory Pollen Allergen Solution-Squibb; Johnson Grass Pollen Allergen Solution-Squibb; June Grass Pollen Allergen Solution-Squibb; Lamb's Quarters Pollen Allergen Solution-Squibb; Marsh Elder Pollen Allergen Solution-Squibb; Mugwort Pollen Allergen Solution-Squibb; Nettle Pollen Allergen Solution-Squibb; Oak Pollen Allergen Solution-Squibb; Orchard Grass Pollen Allergen Solution-Squibb; Perennial Rye Grass Pollen Allergen Solution-Squibb; Pigweed Pollen Allergen Solution-Squibb; Pine Pollen Allergen Solution-Squibb; Poplar Pollen Allergen Solution-Squibb; Ragweed Pollen Allergen Solution-Squibb; Ragweed (Dwarf) Pollen Allergen Solution-Squibb; Ragweed (Giant) Pollen Allergen Solution-Squibb; Redtop Pollen Allergen Solution-Squibb; Russian Thistle Pollen Allergen Solution-Squibb; Rye Pollen Allergen Solution-Squibb; Sandbur Pollen Allergen Solution-Squibb; Sagebrush Pollen Allergen Solution-Squibb; Shadscale Pollen

Allergen Solution-Squibb; Sheep Sorrel Pollen Allergen Solution-Squibb; Slender Ragweed Pollen Allergen Solution-Squibb; Sunflower Pollen Allergen Solution-Squibb, Sweet Vernal Grass Pollen Allergen Solution-Squibb; Timothy Pollen Allergen Solution-Squibb; Western Ragweed Pollen Allergen Solution-Squibb.

The following pollen allergen solutions-Squibb are marketed in treatment sets consisting of:

Set A: ten vials containing for each consecutive dose (1 to 10, inclusive) 0.00005, 0.0001, 0.0002, 0.0004, 0.0008, 0.0016, 0.0032, 0.0064, 0.0128 and 0.025 mg. of pollen nitrogen, respectively, ten vials of sterile diluent with which to make the proper dilution of each dose.

Set B: five vials containing for each consecutive dose (1 to 5, inclusive) 0.00005, 0.0001, 0.0002, 0.0004 and 0.0008 mg. of pollen nitrogen, respectively, five vials of sterile diluent with which to make the proper dilution of each dose.

Set C: five vials containing for each consecutive dose (6 to 10, inclusive) 0.0016, 0.0032, 0.0064, 0.0128 and 0.025 mg. of pollen nitrogen, respectively, five vials of sterile diluent with which to make the proper dilution of each dose.

Set D: five vials (dose 10) each containing 0.025 mg. of pollen nitrogen, five vials of sterile diluent with which to make the proper dilution of each dose.

Bermuda Grass Pollen Allergen Solution-Squibb; June Grass Pollen Allergen Solution-Squibb; Mugwort Pollen Allergen Solution-Squibb; Orchard Grass Pollen Allergen Solution-Squibb; Ragweed Pollen Allergen Solution-Squibb; Sagebrush Pollen Allergen Solution-Squibb; Timothy Pollen Allergen Solution-Squibb; Western Ragweed Pollen Allergen Solution-Squibb.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

Pollen allergen solutions-Squibb are prepared by the following method: The pollen is weighed, extracted with ether, the residue dried and ground in a ball mill with 1 per cent sodium chloride solution for from 12 to 24 hours. The nitrogen in the extract is determined by the Kjeldahl method and the extract diluted with glycerin and 1 per cent sodium chloride solution until the final volume contains 60 per cent of glycerin. The solution is then filtered through a Berkefeld filter, the filtrate tested for sterility and diluted so that each dosage form contains the declared quantity of pollen nitrogen.

POLLEN ANTIGENS-LEDERLE.—Liquids obtained by extracting the protein from the pollen of plants with a liquid consisting of 67 per cent glycerin and 33 per cent saturated solution of sodium chloride.

Actions and Uses.—See preceding article, Allergic Protein Preparations.

Pollen Antigens-Lederle are marketed in the following forms:

Series A: five vials containing for each consecutive dose (1 to 5, inclusive) 2.5, 5, 10, 20 and 35 pollen units, respectively, and five vials of sterile diluent with which to make the proper dilution of each dose.

Series B: five vials containing for each consecutive dose (6 to 10, inclusive) 60, 100, 165, 275 and 450 pollen units, respectively, and five vials of sterile diluent with which to make the proper dilution of each dose.

Series C: five vials containing for each consecutive dose (11 to 15, inclusive) 750, 1,200, 1,800, 2,400 and 3,000 pollen units, respectively, and five vials of sterile diluent with which to make the proper dilution of each dose.

Complete Series: packages containing the 15 doses, described in Series A, B and C.

Manufactured by the Lederle Antitoxin Laboratories, New York. No U. S. patent or trademark.

Annual Salt Bush Pollen Antigen-Lederle; Arizona Ash Pollen Antigen-Lederle; Arizona Walnut Pollen Antigen-Lederle; Bermuda Grass Pollen Antigen-Lederle; Black Walnut Pollen Antigen-Lederle; Careless Weed Pollen Antigen-Lederle; Cocklebur Pollen Antigen-Lederle; Cottonwood Pollen Antigen-Lederle; Giant Ragweed Pollen Antigen-Lederle; Green Sage Pollen Antigen-Lederle; Johnson Grass Pollen Antigen-Lederle; June Grass Pollen Antigen-Lederle (Poa pratensis); Lambs Quarters Pollen Antigen-Lederle; Marsh Elder Pollen Antigen-Lederle; Mountain Cedar Pollen Antigen-Lederle; Mugwort Pollen Antigen-Lederle; Oak Pollen Antigen-Lederle; Olive Pollen Antigen-Lederle; Orchard Grass Pollen Antigen-Lederle; Pasture Sage Pollen Antigen-Lederle; Perennial Rye Grass Pollen Antigen-Lederle; Rabbit Bush Pollen Antigen-Lederle; Ragweed Pollen Antigen-Lederle (Ambrosia elatior); Ragweed Combined Pollen Antigen-Lederle; Redroot Pigweed Pollen Antigen-Lederle; Red Top Pollen Antigen-Lederle; Russian Thistle Pollen Antigen-Lederle; Sage Brush Pollen Antigen-Lederle; Shad Scale Pollen Antigen-Lederle; Sheep Sorrel Pollen Antigen-Lederle; Slender Ragweed Pollen Antigen-Lederle; Southwestern Ragweed Pollen Antigen-Lederle; Spiny Amaranth Pollen Antigen-Lederle; Sweet Vernal Grass Pollen Antigen-Lederle; Timothy Pollen Antigen-Lederle; Western Water Hemp Pollen Antigen-Lederle; Western Ragweed Pollen Antigen-Lederle; Yellow Dock Pollen Antigen-Lederle.

Pollen antigens-Lederle are prepared by grinding the dried pollen with glass dust in a mortar for 2.5 hours, using a diluent composed of 67 per cent of glycerin and 33 per cent of saturated sodium chloride solution to moisten the pollen. Then sufficient of the glycerin-sodium chloride solution is added so that the total volume is such that 1 cc. is equivalent to approximately 30,000 pollen units, the pollen unit having been arbitrarily chosen as the equivalent of 0.001 mg. of pollen. This mixture is shaken for 30 minutes and then kept at 37 C. for 16 hours. It is then shaken for 1 hour, centrifugalized and passed through Buchner and Berkefeld filters.

Pollen antigens-Lederle are standardized by the complement fixation method to determine the active antigenic power of their protein content. Immune serum is obtained from rabbits which have been immunized with a gradually increasing number of units of pollen. Using the same technic for complement fixation as that adopted by the Research Laboratories for the Department of Health, New York, one pollen unit is found to be equivalent approximately to 1-20 of a unit of antigen, taking a unit of antigen as the smallest amount that gives complete fixation in the hemolytic series.

POLLEN EXTRACTS-ARLCO.—Liquids obtained by extracting the proteins from the pollen of various species of plants.

Actions and Uses.—See preceding article, Allergic Protein Preparations.

Dosage.—See preceding article, Allergic Protein Preparations.

Pollen Extracts-Arlco are marketed in sets of five vials representing graduated concentrations, namely, 1 in 10,000, 1 in 5,000, 1 in 1,000, 1 in 500 and 1 in 100, respectively.

Manufactured by The Arlington Chemical Co., Yonkers, N. Y. No U. S. patent or trademark.

Acacia (Scap.) Pollen Extract-Arlco; Alfalfa Pollen Extract-Arlco; Arizona Ash Pollen Extract-Arlco; Arizona Cottonwood Pollen Extract-Arlco; Arizona Walnut Pollen Extract-Arlco; Ash Pollen Extract-Arlco; Aster Pollen Extract-Arlco; Bermuda Grass Pollen Extract-Arlco; Birch Pollen Extract-Arlco; Box Elder Pollen Extract-Arlco; Burning Bush Pollen Extract-Arlco; Burr Ragweed Pollen Extract-Arlco; Burroweed Pollen Extract-Arlco; California Mugwort Pollen Extract-Arlco; California Walnut (Black) Pollen Extract-Arlco; Carelessweed Pollen Extract-Arlco; Carpet Sage Pollen Extract-Arlco; Cherry Pollen Extract-Arlco; Cocklebur Pollen Extract-Arlco; Cosmos Pollen Extract-Arlco; Clover Pollen Extract-Arlco; Corn Pollen Extract-Arlco; Dahlia Pollen Extract-Arlco; Daisy Pollen Extract-Arlco; Dandelion Pollen Extract-Arlco; Dock Pollen Extract-Arlco; Elm Pollen Extract-Arlco; Fleabane (Common) Pollen Extract-Arlco; Golden Glow Pollen Extract-Arlco; Golden Rod Pollen Extract-Arlco; Goosefoot Pollen Extract-Arlco; Greasewood Pollen Extract-Arlco; Hemp Pollen Extract-Arlco; Hickory Pollen Extract-Arlco; Hill Sage Pollen Extract-Arlco; Indian Rice Pollen Extract-Arlco; Indian Wormwood Pollen Extract-Arlco; Johnson Grass Pollen Extract-Arlco; June Grass Pollen Extract-Arlco (Poa Pratensis); Live Oak Pollen Extract-Arlco; Locust Pollen Extract-Arlco; Maple Pollen Extract-Arlco; Marsh Elder Pollen Extract-Arlco; Meadow Fescue Pollen Extract-Arlco; Mexican Tea Pollen Extract-Arlco; Mountain Cedar Pollen Extract-Arlco; Mugwort Pollen Extract-Arlco; Narcissus Pollen Extract-Arlco; Oak Pollen Extract-Arlco; Oat Grass Pollen Extract-Arlco; Olive Pollen Extract-Arlco; Orach Pollen Extract-Arlco; Orchard Grass Pollen Extract-Arlco; Pigweed Pollen Extract-Arlco; Pine Pollen Extract-Arlco; Plantain Pollen Extract-Arlco; Poplar Pollen Extract-Arlco; Prairie Ragweed Pollen Extract-Arlco; Prairie Sage Pollen Extract-Arlco; Privet Pollen Extract-Arlco; Ragweed Pollen Extract-Arlco (Ambrosia trifida); Ragweed Pollen Extract-Arlco (Ambrosia artemisiaefolia); Red Fescue Pollen Extract-Arlco; Red Top Pollen Extract-Arlco; Rose Pollen Extract-Arlco; Russian Thistle Pollen Extract-Arlco; Rye Pollen Extract-Arlco; Rye Grass Pollen Extract-Arlco; Sage Brush Pollen Extract-Arlco; Sea Blite Pollen Extract-Arlco; Shad Scale Pollen Extract-Arlco; Slender Ragweed Pollen Extract-Arlco; Sunflower Pollen Extract-Arlco; Sweet Clover Pollen Extract-Arlco; Sweet Vernal Grass Pollen Extract-Arlco; Sycamore Pollen Extract-Arlco; Thistle Pollen Extract-Arlco; Timothy Pollen Extract-Arlco; Velvet Grass Pollen Extract-Arlco; Walnut Pollen Extract-Arlco; Western Cottonwood Pollen Extract-Arlco; Western Ragweed (Giant) Pollen Extract-Arlco; Wild Sunflower Pollen Extract-Arlco; Winter Fat Pollen Extract-Arlco; Willow Pollen Extract-Arlco; Yellow Daisy Pollen Extract-Arlco.

Pollen extracts-Arlco are prepared by the method of Walker (Am. J. M. Sc. **157**: 409 [March] 1919): To 0.5 Gm. of the dry pollen is added 44 cc. of sterile physiological solution of sodium chloride and the mixture is shaken thoroughly at frequent intervals for twenty-four hours. Sufficient absolute alcohol (7 cc.) is then added to make the alcohol content 14 per cent. The mixture is thoroughly shaken at frequent intervals for twenty-four hours, after which it is centrifugalized at high speed and the supernatant fluid is drawn off with a pipette. This liquid, therefore, consists of the pollen protein dissolved in a 14 per cent alcoholic physiological solution of sodium chloride and it represents, by weight, 1 part of pollen in 100 parts of solvent. This 1 in 100 solution is used as stock and from it other dilutions, such as 1 in 500, 1 in 1,000, 1 in 5,000 and 1 in 10,000 are made. Cresol is added as a preservative.

POLLEN EXTRACTS-CUTTER.—Liquids obtained by extracting the dried pollen of plants with a liquid consisting of 67 per cent of glycerin and 33 per cent of a buffered saline solution.

Actions and Uses.—See preceding article, Allergic Protein Preparations.

Dosage.—See preceding article, Allergic Protein Preparations.

Pollen extracts-Cutter are marketed in complete treatment set packages consisting of three vials representing graduated concentrations, namely, 1 in 10,000, 1 in 1,000 and 1 in 100, respectively; and in single vial packages containing 5 cc. of a 1 : 100 solution.

Manufactured by the Cutter Laboratory, Berkeley, Calif. No U. S. patent or trademark.

Alkali Weed Pollen Extract-Cutter; All Scale Pollen Extract-Cutter; Annual Salt Bush Pollen Extract-Cutter; Arizona Ash Pollen Extract-Cutter; Bermuda Grass Pollen Extract-Cutter; Black Walnut Pollen Extract-Cutter; Box Elder Pollen Extract-Cutter; Burning Bush Pollen Extract-Cutter; Canary Grass Pollen Extract-Cutter; Careless Weed Pollen Extract-Cutter; Coast Sagebrush Pollen Extract-Cutter; Cocklebur Pollen Extract-Cutter; Common Ragweed Pollen Extract-Cutter; Corn Pollen Extract-Cutter; Cottonwood Pollen Extract-Cutter; False Ragweed Pollen Extract-Cutter; Foxtail Pollen Extract-Cutter; Giant Ragweed Pollen Extract-Cutter; Johnson Grass Pollen Extract-Cutter; June Grass Pollen Extract-Cutter; Lamb's Quarters Pollen Extract-Cutter; Mountain Cedar Pollen Extract-Cutter; Marsh Elder Pollen Extract-Cutter;Mugwort Pollen Extract-Cutter; Olive Pollen Extract-Cutter; Orchard Grass Pollen Extract-Cutter; Plantain Pollen Extract-Cutter; Red Root Pigweed Pollen Extract-Cutter; Red Top Pollen Extract-Cutter; Russian Thistle Pollen Extract-Cutter; Rye Grass Pollen Extract-Cutter; Sagebrush Pollen Extract-Cutter; Shadscale Pollen Extract-Cutter; Timothy Pollen Extract-Cutter; Tumbleweed Pollen Extract-Cutter; Velvet Grass Pollen Extract-Cutter; Wild Oat Pollen Extract-Cutter.

Pollen extracts-Cutter are prepared by extracting the dried pollen with a menstruum composed of 67 per cent of glycerin and 33 per cent of an aqueous solution containing potassium dihydrogen phosphate (KH_2PO_4), 0.0908 per cent; sodium phosphate ($Na_2HPO_4.12\ H_2O$). 0.238 per cent; and sodium chloride, 0.85 per cent. The extract is clarified by Berkefeld filtration. The finished liquid is a 1 per cent extract of the dried pollen, each cc. representing 0.01 Gm. of dried pollen.

POLLEN EXTRACTS CONCENTRATED-CUTTER.—Liquids obtained by extracting the dried pollen of plants with a liquid consisting of 67 per cent of glycerin and 33 per cent of a buffered saline solution.

Actions and Uses.—See preceding article, Allergic Protein Preparations.

Dosage.—See preceding article, Allergic Protein Preparations.

Pollen extracts concentrated-Cutter are marketed in single vial packages containing 5 cc.

Manufactured by the Cutter Laboratory, Berkeley, Calif. No U. S. patent or trademark.

Alkali Weed Pollen Extract Concentrated-Cutter; Allscale Pollen Extract Concentrated-Cutter; Annual Saltbush Pollen Extract Concentrated-Cutter; Arizona Ash Pollen Extract Concentrated-Cutter; Bermuda Grass Pollen Extract Concentrated-Cutter; Black Walnut Pollen Extract Concentrated-Cutter; Box Elder Pollen Extract Concentrated-Cutter; Burning Bush Pollen Extract Concentrated-Cutter; Canary Grass Pollen Extract Concentrated-Cutter; Careless Weed Pollen Extract Concentrated-Cutter; Coast Sagebrush Pollen Extract Concentrated-Cutter; Cocklebur Pollen Extract Concentrated-Cutter; Common Ragweed Pollen Extract Concentrated-Cutter; Corn Pollen Extract Concentrated-Cutter; Cottonwood Pollen Extract Concentrated-Cutter; False Ragweed Pollen Extract Concentrated-Cutter; Foxtail Grass Pollen Extract Concentrated-Cutter; Giant Ragweed Pollen Extract Concentrated-Cutter; Johnson Grass Pollen Extract Concentrated-Cutter; June Grass Pollen Extract Concentrated-Cutter; Lamb's Quarters Pollen Extract Concentrated-Cutter; Marsh Elder Pollen Extract Concentrated-Cutter; Mountain Cedar Pollen Extract Concentrated-Cutter; Mugwort Pollen Extract Concentrated-Cutter; Oak Pollen Extract Concentrated-Cutter; Olive Pollen Extract Concentrated-Cutter; Orchard Grass Pollen Extract Concentrated-Cutter; Plantain Pollen Extract Concentrated-Cutter; Red Root Pigweed Pollen Extract Concentrated-Cutter; Red Top Pollen Extract Concentrated-Cutter; Russian Thistle Pollen Extract Concentrated-Cutter; Rye Grass Pollen Extract Concentrated-Cutter; Sagebrush Pollen Extract Concentrated-Cutter; Shad Scale Pollen Extract Concentrated-Cutter; Timothy Pollen Extract Concentrated-Cutter; Tumbleweed Pollen Extract Concentrated-Cutter; Velvet Grass Pollen Extract Concentrated-Cutter; Western Ragweed Pollen Extract Concentrated-Cutter; Western Waterhemp Pollen Extract Concentrated-Cutter; Wild Oat Pollen Extract Concentrated-Cutter.

Pollen extracts concentrated-Cutter are prepared by extracting the dried pollen with a menstruum composed of 67 per cent of glycerin and 33 per cent of an aqueous solution containing potassium dihydrogen phosphate (KH_2PO_4), 0.0908 per cent; sodium phosphate ($Na_2HPO_4 \cdot 12\ H_2O$), 0.238 per cent, and sodium chloride, 0.85 per cent. The extract is clarified by Berkefeld filtration. The finished liquid is a 3 per cent extract of the dried pollen, each cubic centimeter representing 0.03 Gm. of dried pollen.

POLLEN EXTRACTS-HOLLISTER-STIER. — Liquids obtained by extracting the dried pollen of plants with a liquid consisting of 48 per cent of glycerin, 5 per cent of sodium chloride and 47 per cent distilled water.

Actions and Uses.—See preceding article, Allergic Protein Preparations.

Dosage.—See preceding article, Allergic Protein Preparations.

Pollen extracts-Hollister-Stier are marketed in treatment sets of five vials containing, respectively, 20, 100, 1,000, 5,000 and 10,000 units per cubic centimeter accompanied by three vials of physiological solution of sodium chloride for diluting the extract; in treatment sets of thirty vials, twenty containing 1, 3, 5, 7, 10, 15, 30, 50, 70, 100, 150, 200, 300, 400, 500, 600, 700, 800, 900, 1,000, and ten each containing 1,000 units, accompanied by thirty vials of physiological solution of sodium chloride for diluting the extract.

Manufactured by the Hollister-Stier Laboratories, Spokane, Washington. No U. S. patent or trademark.

Alder Pollen Extract-Hollister-Stier; Aspen Pollen Extract-Hollister-Stier; Atriplex Pollen Extract-Hollister-Stier; Awnless Brome Grass Pollen Extract-Hollister-Stier; Blue Bunch Grass Pollen Extract-Hollister-Stier; Box Elder Pollen Extract-Hollister-Stier; Canada Blue Grass Pollen Extract-Hollister-Stier; Cheat Pollen Extract-Hollister-Stier; Common Sagebrush Pollen Extract-Hollister-Stier; Crested Koeleria Pollen Extract-Hollister-Stier; Dandelion Pollen Extract-Hollister-Stier; Eastern Ragweed Pollen Extract-Hollister-Stier; English Plantain Pollen Extract-Hollister-Stier; Giant Poverty Weed Pollen Extract-Hollister-Stier; Kentucky Blue Grass Pollen Extract-Hollister-Stier; Lamb's Quarters Pollen Extract-Hollister-Stier; Mugwort Pollen Extract-Hollister-Stier; Orchard Grass Pollen Extract-Hollister-Stier; Perennial Rye Grass Pollen Extract-Hollister-Stier; Quack Grass Pollen Extract-Hollister-Stier; Red Top Pollen Extract-Hollister-Stier; Redroot Pigweed Pollen Extract-Hollister-Stier; Russian Thistle Pollen Extract-Hollister-Stier; Sandberg's June Grass Pollen Extract-Hollister-Stier; Sheep Sorrel Pollen Extract-Hollister-Stier; Spring Birch Pollen Extract-Hollister-Stier; Timothy Pollen Extract-Hollister-Stier; Velvet Grass Pollen Extract-Hollister-Stier; Western Ragweed Pollen Extract-Hollister-Stier; Willow Pollen Extract-Hollister-Stier.

Pollen extracts-Hollister-Stier are prepared by extracting the dried pollen with a menstruum composed of 48 per cent of glycerin, 5 per cent of sodium chloride and 47 per cent distilled water. The extract is clarified by Berkefeld filtration. The finished liquid is a 1 per cent extract of the dried pollen, each cubic centimeter representing 10,000 pollen units; 1 unit corresponding to 0.001 mg. of dried pollen.

POLLEN EXTRACTS-MULFORD.—Pollen Atopen Solutions-Mulford.—Liquids obtained by extracting the proteins from the pollen of plants and standardizing the solution by estimating the amount of protein contained in them: 1 unit equals 0.001 mg. of pollen protein. Preserved with 0.5 per cent of phenol.

Actions and Uses.—See preceding article, Allergic Protein Preparations.

Dosage.—See preceding article, Allergic Protein Preparations.

The following pollen extracts-Mulford are marketed in 5 cc. vials containing 500 units per cubic centimeter:

Ash Tree Pollen Extract-Mulford; Alder Pollen Extract-Mulford; Alfalfa Pollen Extract-Mulford; Annual Sage Pollen Extract-Mulford; Apple Pollen Extract-Mulford; Aster Pollen Extract-Mulford; Bermuda Grass Pollen Extract-Mulford; Blue Beech Pollen Extract-Mulford; Boneset Pollen Extract-Mulford; Box Elder Pollen Extract-Mulford; Brome Grass Pollen Extract-Mulford; Burning Bush Pollen Extract-Mulford; Burweed Marsh Elder Pollen Extract-Mulford; Buttercup Pollen Extract-Mulford; California Mugwort Pollen Extract-Mulford; Canary Grass Pollen Extract-Mulford; Careless Weed Pollen Extract-Mulford; Cedar Tree Pollen Extract-Mulford; Clover Pollen Extract-Mulford; Coast Sage Pollen Extract-Mulford; Cocklebur Pollen Extract-Mulford; Corn Pollen Extract-Mulford; Cosmos Pollen Extract-Mulford; Cottonwood Tree Pollen Extract-Mulford; Crab Grass Pollen Extract-Mulford; Dahlia Pollen Extract-Mulford; Daisy Pollen Extract-Mulford; Dandelion Pollen Extract-Mulford; Dock Pollen Extract-Mulford; Dragon Sage Pollen Extract-Mulford; Elm Tree Pollen Extract-Mulford; English Plantain Pollen Extract-Mulford; False Ragweed Pollen Extract-Mulford; Fescue Pollen Extract-Mulford; Golden Glow Pollen Extract-Mulford; Goldenrod Pollen Extract-Mulford; Hickory Tree Pollen Extract-Mulford; High Ragweed Pollen Extract-Mulford; Johnson Grass Pollen Extract-Mulford; June Grass Pollen Extract-Mulford; Low Ragweed Pollen Extract-Mulford Maple Pollen Extract-Mulford; Marsh Elder Pollen Extract-Mulford; Mexican Tea Pollen Extract-Mulford; Milo Maize Pollen Extract-Mulford; Mock Orange Pollen Extract-Mulford; Mountain Cedar Pollen Extract-Mulford; Mugwort Pollen Extract-Mulford; Oak Tree Pollen Extract-

Mulford; Oat Pollen Extract-Mulford; Olive Pollen Extract-Mulford; Orchard Grass Pollen Extract-Mulford; Peach Tree Pollen Extract-Mulford; Pecan Tree Pollen Extract-Mulford; Perennial Rye Grass Pollen Extract-Mulford; Pine Tree Pollen Extract-Mulford; Plantain Pollen Extract-Mulford; Poverty Weed Pollen Extract-Mulford; Prairie Grass Pollen Extract-Mulford; Privet Pollen Extract-Mulford; Quack Grass Pollen Extract-Mulford; Rabbit Brush Pollen Extract-Mulford; Redroot Pigweed Pollen Extract-Mulford; Redtop Pollen Extract-Mulford; Rose Pollen Extract-Mulford; Russian Thistle Pollen Extract-Mulford; Rye Pollen Extract-Mulford; Sagebrush Pollen Extract-Mulford; Salt Bush Pollen Extract-Mulford; Shad Scale Pollen Extract-Mulford; Sheep Sorrel Pollen Extract-Mulford; Slender Ragweed Pollen Extract-Mulford; Spring Amaranth Pollen Extract-Mulford; Sudan Grass Pollen Extract-Mulford; Sugar Beet Pollen Extract-Mulford; Sunflower Pollen Extract-Mulford; Sweet Vernal Grass Pollen Extract-Mulford; Velvet Grass Pollen Extract-Mulford; Walnut Tree Pollen Extract-Mulford; Water Hemp Pollen Extract-Mulford; Western Giant Ragweed Pollen Extract-Mulford; Western Ragweed Pollen Extract-Mulford; Wheat Pollen Extract-Mulford; Wild Oats Pollen Extract-Mulford; Willow Tree Pollen Extract-Mulford; Winter Grass Pollen Extract-Mulford; Yellow Foxtail Grass Pollen Extract-Mulford.

The following pollen extracts-Mulford are marketed in 5 cc. vials containing 500 units per cubic centimeter; in packages of three 5 cc. vials containing, respectively, 250, 500 and 1,000 units per cubic centimeter; and in treatment sets consisting of:

First series: five glass syringes (doses 1 to 5, inclusive) containing, respectively, 25 units, 50 units, 75 units, 100 units and 150 units.

Second series: five glass syringes (doses 6 to 10, inclusive) containing, respectively, 200 units, 250 units, 300 units, 350 units and 400 units.

Third series: five glass syringes (doses 11 to 15, inclusive) containing, respectively, 500 units, 600 units, 700 units, 800 units and 1,000 units.

Fourth Series: Five glass syringes (doses 16 to 20, inclusive), each containing 1,000 protein units.

Complete series: fifteen glass syringes containing doses 1 to 15 inclusive, described in the First, Second and Third Series.

Lamb's Quarters Pollen Extract-Mulford; Ragweed Pollen Extract (Fall)-Mulford; Timothy Pollen Extract (Spring)-Mulford; Wormwood Pollen Extract-Mulford.

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

The pollen, after being dried, is ground in a ball mill to destroy the cell membranes. It is then extracted with water containing phenol, 0.5 per cent and the amount of soluble proteins in the extract is estimated by a Kjeldahl nitrogen determination. The preparation is then standardized according to the protein (nitrogen) content, sterilized by Berkefeld filtration and subjected to tests for sterility. The nitrogen content, multiplied by the factor 6.25 gives the protein content, and this result divided by 0.001 gives the number of protein units.

POLLEN EXTRACTS (GLYCERO-SALINE)-MULFORD.—Liquids obtained by extracting the dried pollen of plants with a liquid consisting of 66⅔ per cent of glycerin and 33⅓ per cent of saturated sodium chloride solution.

Actions and Uses.—See preceding article, Allergic Protein Preparations.

Dosage.—See preceding article, Allergic Protein Preparations.

Pollen extracts (glycero-saline)-Mulford are marketed in bulk treatment packages consisting of one vial containing 1 cc. of the glycero-saline pollen extract and two 10 cc. vials of physiological solution of sodium chloride containing 0.5 per cent of phenol for making dilutions, and in treatment sets consisting of:

First series: five vials (doses 1 to 5, inclusive) containing, respectively, 25 protein units, 50 protein units, 75 protein units, 100 protein units and 150 protein units, accompanied by five vials of sterile distilled water containing 0.5 per cent of phenol.

Second series: five vials (doses 6 to 10, inclusive) containing, respectively, 200 protein units, 250 protein units, 375 protein units, 500 protein units and 625 protein units, accompanied by five vials of sterile distilled water containing 0.5 per cent of phenol.

Third series: five vials (doses 11 to 15, inclusive) containing, respectively, 750 protein units, 875 protein units, 1,000 protein units, 1,125 protein units and 1,250 protein units, accompanied by five vials of sterile distilled water containing 0.5 per cent of phenol.

Complete series: fifteen vials containing doses 1 to 15 inclusive, described in the First, Second and Third series, accompanied by fifteen vials of sterile distilled water containing 0.5 per cent of phenol.

Fourth series: five vials (doses 16 to 20, inclusive) each containing 1,250 protein units, accompanied by five vials of sterile distilled water containing 0.5 per cent of phenol.

Lamb's Quarters Pollen Extract (Glycero-Saline)-Mulford; Ragweed Pollen Extract (Glycero-Saline)-Mulford; Timothy Pollen Extract (Glycero-Saline)-Mulford; Wormwood Pollen Extract (Glycero-Saline)-Mulford.

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

A solution containing 66⅔ per cent of glycerin and 33⅓ per cent of saturated sodium chloride solution is thoroughly mixed with the pollen in a quantity to make a 10 per cent pollen suspension. The mixture is agitated occasionally for about seven days, after which the solid residue is removed by filtration. Each cubic centimeter represents the substances extracted from 0.1 Gm. of pollen (100,000 pollen units, approximately equivalent to 25,000 protein units).

POLLEN EXTRACTS-SWAN-MYERS.—Liquids obtained by extracting the protein from the pollen of plants with a liquid consisting of 67 per cent glycerin and 33 per cent of a buffered salt solution.

Actions and Uses.—See preceding article, Allergic Protein Preparations.

Dosage.—See preceding article, Allergic Protein Preparations.

Pollen Extracts-Swan-Myers are marketed in the following forms:

Series I: five vials containing for each consecutive dose (1 to 5, inclusive) 5, 10, 20, 40 and 70 pollen units, respectively, accompanied by a vial containing three 0.025 Gm. (⅜ grain) capsules ephedrine hydrochloride.

Series II: five vials containing for each consecutive dose (6 to 10, inclusive) 100, 200, 400, 700 and 1,000 pollen units, respectively, accompanied by a vial containing three 0.025 Gm. (⅜ grain) capsules ephedrine hydrochloride.

Series III: five vials containing for each consecutive dose (11 to 15, inclusive) 1,500, 2,000, 3,000, 3,500 and 4,000 pollen units, respectively, accompanied by a vial containing three 0.025 Gm. (⅜ grain) capsules ephedrine hydrochloride.

Complete series: packages containing the 15 doses, described in Series I, II and III.

Packages of 1 vial containing 4,000 pollen units.

Ragweed Pollen (Ambrosia Elatior and Ambrosia Trifida) Extract-Swan-Myers; Timothy Pollen Extract-Swan-Myers.

Manufactured by Swan-Myers Company, Indianapolis, Ind. No U. S. patent or trademark.

Pollen extracts-Swan-Myers are prepared by grinding dried pollen in a ball mill with a liquid composed of 67 per cent of glycerin and 33 per cent of a solution containing sodium chloride, 5 Gm., and sodium bicarbonate, 2.7 Gm., in distilled water, 1,000 cc. Sufficient of the glycerin-buffered salt solution is added so that the total volume is such that each cc. represents 20,000 units; 1 unit corresponding to 0.001 mg. of dried pollen. This mixture is filtered through paper pulp and then through a Berkefeld filter. It is tested for sterility before diluting, after dilution and after filling.

PROTEIN EXTRACTS-MULFORD.—Atopen Solutions-Mulford.—Liquids obtained by extracting the protein of substances believed to be the cause of specific sensitization.

Actions and Uses.—See preceding article, Allergic Protein Preparations.

Dosage.—See preceding article, Allergic Protein Preparations.

Protein Extracts-Mulford are marketed in 5 cc. vials containing 500 "protein units" per cc.

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

Almond Protein Extract-Mulford[4]; *Apple Protein Extract-Mulford*[1]; *Asparagus Protein Extract-Mulford*[1]; *Banana Protein Extract-Mulford*[1]; *Barley Protein Extract-Mulford*[7]; *Bean (Lima) Protein Extract-Mulford*[7]; *Bean (Navy) Protein Extract-Mulford*[7]; *Bean (String) Protein Extract-Mulford*[1]; *Beef Protein Extract-Mulford*[2]; *Beet Protein Extract-Mulford*[1]; *Buckwheat Protein Extract-Mulford*[7]; *Butternut Protein Extract-*

Mulford[2]; *Cabbage Protein Extract-Mulford*[1]; *Cantaloupe Protein Extract-Mulford*[1]; *Carrot Protein Extract-Mulford*[1]; *Cat Hair Protein Extract-Mulford*[8]; *Cattle Dander Protein Extract-Mulford*[8]; *Cauliflower Protein Extract-Mulford*[1]; *Celery Protein Extract-Mulford*[1]; *Cheese Protein Extract-Mulford*[2, 4]; *Cherry Protein Extract-Mulford*[1]; *Chicken Protein Extract-Mulford*[2]; *Chicken Feather Protein Extract-Mulford*[8]; *Clam Protein Extract-Mulford*[2]; *Cocoanut Protein Extract-Mulford*[2]; *Cocoa Protein Extract-Mulford*[1]; *Codfish Protein Extract-Mulford*[2]; *Coffee Protein Extract-Mulford*[7]; *Corn Protein Extract Mulford*[7]; *Crab Protein Extract-Mulford*[2, 4]; *Cucumber Protein Extract-Mulford*[1]; *Dog Hair Protein Extract-Mulford*[8]; *Duck Feathers Protein Extract-Mulford*[8]; *Eggplant Protein Extract-Mulford*[1]; *Egg White Protein Extract-Mulford*[5]; *Egg Yolk Protein Extract-Mulford*[5]; *Flaxseed Protein Extract-Mulford*[11]; *Garlic Protein Extract-Mulford*[2]; *Ginger Protein Extract-Mulford*[2, 4]; *Goose Feather Protein Extract-Mulford*[8]; *Goose Protein Extract-Mulford*[2]; *Grape Protein Extract-Mulford*[1]; *Grapefruit Protein Extract-Mulford*[1]; *Guinea-Pig Hair Protein Extract-Mulford*[8]; *Haddock Protein Extract-Mulford*[2]; *Halibut Protein Extract-Mulford*[2]; *Herring Protein Extract-Mulford*[2]; *Horse Dander Protein Extract-Mulford*[8]; *Horse Serum Protein Extract-Mulford*[13]; *Kapok Protein Extract-Mulford*[12]; *Lamb Protein Extract-Mulford*[2]; *Lettuce Protein Extract-Mulford*[1]; *Lobster Protein Extract-Mulford*[2]; *Mackerel Protein Extract-Mulford*[2]; *Milk Protein Extract-Mulford*[9]; *Mushroom Protein Extract-Mulford*[1]; *Mustard Protein Extract-Mulford*[2, 4]; *Nutmeg Protein Extract-Mulford*[2, 4]; *Oat Protein Extract-Mulford*[7]; *Onion Protein Extract-Mulford*[1]; *Orange Protein Extract-Mulford*[1]; *Orris Root Protein Extract-Mulford*[1]; *Oyster Protein Extract-Mulford*[2]; *Paprika Protein Extract-Mulford*[2]; *Parsley Protein Extract-Mulford*[14]; *Parsnip Protein Extract-Mulford*[14]; *Peach Protein Extract-Mulford*[14]; *Peanut Protein Extract-Mulford*[4]; *Pea Protein Extract-Mulford*[7]; *Pear Protein Extract-Mulford*[14]; *Pecan Protein Extract-Mulford*[2]; *Pepper (Black) Protein Extract-Mulford*[4]; *Pineapple Protein Extract-Mulford*[1]; *Pork Protein Extract-Mulford*[2]; *Potato Protein Extract-Mulford*[7]; *Prune Protein Extract-Mulford*[14]; *Rabbit Hair Protein Extract-Mulford*[8]; *Raisin Protein Extract-Mulford*[14]; *Rice Protein Extract-Mulford*[7]; *Rice Powder (Polish) Protein Extract-Mulford*[7]; *Rye Protein Extract-Mulford*[7]; *Salmon Protein Extract-Mulford*[2]; *Shrimp Protein Extract-Mulford*[2]; *Sole Protein Extract-Mulford*[2]; *Spinach Protein Extract-Mulford*[1]; *Squash Protein Extract-Mulford*[1]; *Strawberry Protein Extract-Mulford*[1]; *Sheep's Wool Protein Extract-Mulford*[8]; *Sweet Potato Protein Extract-Mulford*[1]; *Tea Protein Extract-Mulford*[8]; *Tomato Protein Extract-Mulford*[1]; *Tuna Fish Protein Extract-Mulford*[2]; *Turnip Protein Extract-Mulford*[14]; *Veal Protein Extract-Mulford*[2]; *Walnut (Black) Protein Extract-Mulford*[2]; *Walnut Protein Extract-Mulford*[4]; *Wheat Protein Extract-Mulford*[7].

The following product is marketed in 5 cc. vials containing 250 "protein units" per cubic centimeter:

Duck Protein Extract-Mulford.[2]

Protein Extracts-Mulford are prepared from various substances, and extracted with a buffered salt solution composed of sodium chloride 25 Gm., sodium bicarbonate 12.5 Gm., phenol 0.5 Gm., one liter of distilled water. The finished product is adjusted to contain 500 "protein units" per cc.

Products marked (1) are prepared by the following method: The peel, if any, is removed, the substance is minced in a grinder and the juice is collected; 0.5 per cent phenol is added, also a thin layer of toluene. The mass is thoroughly shaken and allowed to stand for one week. It is then filtered and sterilized by Berkefeld filtration.

Products marked (2) are prepared by the following method: To the minced substance acetone is added. It is shaken thoroughly and transferred to a filter. This process is repeated until all traces of fat are removed. The acetone is then evaporated off, and the dried residue sifted and extracted with the buffered salt solution.

Products marked (3) are prepared by the following method: The substance is subjected to heat at 65 C. for one hour in a 0.2 per cent solution of sodium hydroxide. After cooling, it is strained through cheese cloth, filtered, and precipitated with acetic acid (36 per cent). The precipitate collected is redissolved in 0.2 per cent solution of sodium hydroxide, filtered, and again precipitated with acetic acid. The final precipitate is dried, ground in a mortar, and sifted through fine bolting cloth. The dried substance is extracted with the buffered salt solution.

Products marked (4) are prepared by the following method: The shell, if any, is removed, the substance is minced (when required) and the oil extracted with ether. The residue is ground in a mortar and sifted through fine bolting cloth. It is then extracted with the buffered salt solution.

Products marked (5) are prepared by the following method: The whites and yolks are separated and each coagulated with acetone. The respective coagulates are ground, dried and sifted through fine bolting cloth. The dried material is extracted with the buffered salt solution.

Products marked (7) are prepared by the following method: The substance is treated one hour with a 0.2 per cent solution of sodium hydroxide. It is then strained through cheese cloth, filtered, and precipitated with acetic acid (36 per cent). The precipitate collected is redissolved in 0.2 per cent solution of sodium hydroxide, filtered, and again precipitated with acetic acid. The final precipitate is dried, ground in a mortar, sifted through fine bolting cloth, and extracted with buffered salt solution.

Products marked (8) are prepared by the following method: The substance is extracted with chloroform, dried, ground in a mortar, and sifted through fine bolting cloth. It is then extracted with the buffered salt solution.

Products marked (9) are prepared by the following method: The substance is precipitated with acetic acid (36 per cent). The precipitate is collected, dried, ground in a mortar, and sifted through fine bolting cloth. The dried material is extracted with the buffered salt solution.

Products marked (11) are prepared by the following method: The substance is ground, washed with ether, extracted with 0.2 per cent solution of sodium hydroxide, filtered and precipitated with acetic acid. The precipitate is dried and powdered, and extracted with the buffered salt solution.

Products marked (12) are prepared by the following method: The fiber is extracted with 0.2 per cent. solution of sodium hydroxide at 65 C. for four hours, filtered, and precipitated with acetic acid. The precipitate is dried, powdered, and extracted with the buffered salt solution.

The product marked (13) is prepared by the following method: A sterile serum of the blood of horses is passed through a Berkefeld filter.

Products marked (14) are prepared by the following method: The substance is minced in a grinder and is extracted with buffered salt solution.

Protein Extracts-Mulford are tested and standardized in terms of "protein units." The unit is fixed at 0.001 mg. protein. The amount of protein per cc. is determined by the Kjeldahl method. The amount of nitrogen found is multiplied by 6.25, and the result divided by 0.001 to obtain the number of protein units.

ALUMINUM COMPOUNDS

Several of the compounds of aluminum are official, including the ordinary alum or alumen, U. S. P. Aluminum acetate, aluminum aceticotartrate and aluminum subacetate are used in the form of solutions and are described in the National Formulary as Solution of Aluminum Acetate, Solution of Aluminum Acetico-Tartrate and Solution of Aluminum Subacetate.

The aluminum compounds are used for their astringent action. Since they are but little absorbed, they are relatively nontoxic.

Compounds of aluminum are astringent because of their property of precipitating albumin. The exsiccated alum is more energetic, not only because it contains a larger proportion of alum than the crystalline, but also because it absorbs water from the tissue at the same time. The acetate is milder than the sulphate, as is usual with metallic salts.

The aluminum compounds are not so astringent as the corresponding lead salts, but they may exert an irritant and even caustic action when used in concentrated solutions or in the form of the exsiccated (burnt) alum. When swallowed in overdoses in such concentrated form, they may cause gastritis and diarrhea. Alum is sometimes used as an emetic.

The aluminum compounds are slightly antiseptic, a property which goes with their astringency. Some of the organic compounds are said to be more actively antiseptic than the inorganic.

Several proprietary preparations, consisting of aluminum combined with organic acids, have been introduced with a view to utilizing the astringent and antiseptic properties of their components. Many of these possess no special advantages and have fallen into disuse, or have been largely replaced by others of a more or less similar nature.

ALUM.—For description see the U. S. Pharmacopeia and Useful Drugs under Alumen.

Stypsticks, Stypstick Applicators and Special Stypstick Applicators (Alum 75 per cent and potassium nitrate 25 per cent): Wooden sticks, 3.8, 14.0, 16.5 and 30.5 cm. (1½, 5½, 6½ and 12 inches) long, respectively, tipped with a mixture of alum 75 per cent and potassium nitrate 25 per cent. Each stick is to be used but once.

Prepared by Tappan Zee Surgical Company, Nyack, N. Y. No U. S. patent or trademark.

ALUMNOL. — Alumini Naphtholsulphonas. — Aluminum Betanaphthol-Disulphonate. — $Al_2(C_{10}H_5.OH.(SO_3)_2)_3$. — The aluminum salt of betanaphthol-disulphonic acid.

Actions and Uses.—Alumnol is used as a mild antiseptic and in concentrated solutions as an irritant or caustic. It is used for the destruction of the gonococcus, especially in cases of gonorrhea in women in which the endometrium is affected.

Dosage.—As a surgical antiseptic, in from 0.5 to 3 per cent solutions; in gynecology, in from 2 to 5 per cent solutions; in otology and laryngology, either as a powder or in from 0.25 to 1 per cent solution as douches, washes or gargles; as a cautery, in from 10 to 20 per cent solution.

Manufactured by Farbwerke, vorm. Meister, Lucius & Bruening, Hoechst a.M., Germany (H. A. Metz Laboratories, Inc., distributor). U. S. trademark 173,434.

Alumnol is a fine, nearly white, nonhygroscopic powder. It is soluble in 1.5 parts of water, soluble in glycerin, sparingly soluble in alcohol an insoluble in ether. An aqueous solution is slightly fluorescent and produces a faintly acid reaction. When dried, it loses about 9 per cent of water, and, when exposed to the air, it is darkened in consequence of its reducing properties. It is precipitated from solution by albuminous and gelatinous bodies; but these precipitates are redissolved in excess of the latter bodies. It is decomposed by salts of silver or other reducible salts, by alkalis and by ammoniacal compounds.

Dissolve about 1 Gm. of aluminol in 10 cc. of water: the solution is clear. Acidulate with hydrochloric acid: the liquid becomes at most only slightly turbid. Add a few drops of potassium ferrocyanide solution: the liquid is tinted slightly bluish. On the addition of diluted sulphuric acid or of ammonium oxalate solution to an aqueous solution of almunol, no precipitate is formed.

Incinerate about 2 Gm. of alumnol, accurately weighed: the amount of ash (alumina) is 12.7 per cent.

ANESTHETICS

Anesthetics, General

ETHYL CHLORIDE.—For description see the U. S. Pharmacopeia and Useful Drugs under Aethylis Chloridum.

Kelene.—A brand of ethyl chloride-U. S. P., supplied in a special form of container.

Manufactured by Fries Bros., New York (Merck & Co., Inc., Rahway, N. J.).

ETHYLENE FOR ANESTHESIA.—Aethylenum pro narcosi.—It contains not less than 98 per cent by volume of ethylene ($CH_2:CH_2$).

Actions and Uses.—Animal experiments by W. E. Brown (*Canadian M. A. J.,* March, 1923, p. 210), Luckhardt and Carter (J. A. M. A., March 17, 1923, p. 765) indicate that ethylene has a direct action on the nervous system when a concentration of 90 per cent ethylene and 10 per cent oxygen or less is used, that the motor reflexes are abolished with this concentration and that the phenomena produced by the undiluted gas are partly asphyxial, which effect can be removed by addition of oxygen to the ethylene itself.

Trials on human subjects have confirmed the anesthetic and analgesic value of ethylene as demonstrated on animals. Deep surgical anesthesia is stated to be produced easily, and analgesia comes on readily and apparently long before surgical anesthesia is established. Given with oxygen, it has been found more powerful than nitrous oxide and in most instances as effective as ether; unlike ether it causes no respiratory irritation and does not promote salivary secretion.

A considerable number of trials give promise that ethylene is of value for the production of surgical anesthesia and that it has advantages over nitrous oxide. These advantages are stated to be equally rapid but more pleasant induction, satisfactory relaxation without cyanosis or sweating, and rapid recovery. The disadvantages of ethylene are the odor, which is slightly offensive to some, its inflammability and apparently an increased oozing of the wounds during its use. So far, no contraindications to its use have been discovered.

Dosage.—Ethylene for anesthesia is supplied in compressed state in metal cylinders. For use the gas is passed into an inhalation apparatus and is then inhaled with or without admixture of oxygen. The concentration employed for surgical anesthesia is generally 90 per cent ethylene and 10 per cent oxygen, though after a prolonged period of anesthesia, a deep anesthetic state may be maintained on 80 per cent ethylene. To avoid accidental explosion, ethylene for anesthesia must not be brought in contact with a naked flame or an electric spark; it should not, therefore, be used in the vicinity of electrical devices, cauteries, high frequency apparatus, etc.; switches for electric lights, fans, etc., should not be operated unless they are placed outside of the room.

Ethylene for anesthesia is a colorless gas possessing a slightly sweet odor and taste which is offensive to some. It is somewhat lighter than air. Pure ethylene is solid at below —169.4 C. and boils at —103.9 C. The gas is inflammable and a mixture of it and oxygen explodes when brought in contact with a flame or an electric spark.

One volume of ethylene dissolves in about 4 volumes of water at 0 C. and in 7 volumes at 20 C., and in about one-half volume of alcohol at 25 C. It is also soluble in ether.

Pass 1,000 cc. of ethylene for anesthesia measured under normal atmospheric pressure at about 25 C. through 50 cc. of barium hydroxide solution at a rate not exceeding two bubbles per second: not more than an opalescent turbidity is produced (*carbon dioxide*).

Pass 1,000 cc. of the gas through 50 cc. of distilled water to which 2 drops of methyl red solution has been added: the color of the liquid is not changed (*acids; sulphur dioxide*).

Pass 1,000 cc. of the gas under the condition prescribed in the preceding test through 15 cc. of silver ammonium nitrate solution: no turbidity or darkening is produced (*acetylene, phosphine, aldehyde, hydrogen sulphide*).

Transfer 250 cc. of the gas to a suitable container; add 2.5 cc. of diluted blood (1 part blood to 20 parts of water), avoiding admixture of air as far as possible. Agitate thoroughly the contents for fifteen minutes. Transfer the blood solution to a small test tube, add 0.04 Gm. of a mixture of equal parts of pyrogallic acid and tannic acid. Shake the contents, allow to stand thirty to forty-five minutes: the precipitate assumes a gray-brown color (*absence of carbon monoxide*). If carbon monoxide is present, the precipitate will remain red, the intensity of the color depending on the amount of carbon monoxide in the sample.

Pass 1,000 to 1,500 cc. of ethylene for anesthesia measured accurately under normal atmospheric pressure and at 25 C. into a suitable gas pipet containing either fuming sulphuric acid or bromine water: the residual gas (after treatment with potassium hydroxide solution to absorb the sulphur trioxide) is not greater than 2 per cent of the volume of ethylene used (corresponding to not less than 98 per cent of ethylene). When the residual gas (after removal of oxygen by alkaline pyrogallol solution) is treated with freshly prepared acid cuprous chloride solution (15 Gm. of cuprous oxide in 100 cc. of hydrochloric acid, U. S. P.), no contraction of volume should be noted (*carbon monoxide*). (Note.—If mercury is used as sealing liquid in the buret and hydrogen chloride vapors are present, the gas should be passed over potassium hydroxide before making final reading.)

Ethylene-Cheney.—A brand of ethylene for anesthesia-N. N. R.

The Cheney Chemical Co., Cleveland, distributor. No U. S. patent or trademark.

Ethylene-C. L. P.—A brand of ethylene for anesthesia-N. N. R.

Certified Laboratory Products, Glendale, Calif., distributor. No U. S. patent or trademark.

Ethylene for Anesthesia (Kansas City Oxygen Gas Company).—A brand of ethylene for anesthesia-N. N. R.

Kansas City Oxygen Gas Company, Kansas City, distributor. No U. S. patent or trademark.

Lennox Ethylene.—A brand of ethylene for anesthesia-N. N. R.

Ohio Chemical and Manufacturing Co., Cleveland, distributor. No U. S. patent or trademark.

METHYL CHLORIDE.—Methylis Chloridum.—CH_3Cl.—The hydrochloric acid ester of methyl alcohol. In the compressed state, methyl chloride is a colorless liquid, having an ethereal odor, and a sweet taste.

Actions and Uses.—By its evaporation a temperature of —23 C. is produced, while if evaporation is accelerated by means of a current of air a temperature of —55 C. may easily be reached. On account of this property its use requires caution, since it is liable to produce blisters. The diluted vapor is said to be nonpoisonous. Methyl chloride is said to be an efficient general anesthetic, which has practically no influence on the circulation, but fails to produce complete muscular relaxation. It is used as a general anesthetic mixed with ethyl chloride and ethyl bromide.

Dosage.—When methyl chloride is sprayed on the skin, the part should be somewhat protected by a thin layer of cotton wool. When the anesthetic is used locally, cotton wool soaked in liquid methyl chloride may be applied to the skin over the painful area, but care should be taken that blisters are not formed. In order to avoid this, a mixture with ethyl chloride has been recommended.

Methyl chloride is insoluble in water, more readily soluble in alcohol, freely soluble in ether and chlorform, and also in acetic acid. It should be neutral to litmus paper. Pure methyl chloride has a specific gravity of 0.99145 at —23.7 C. It burns in air with a greenish flame, though it is not highly inflammable. The neutral solution is not precipitated by solution of silver nitrate, nor is there any reaction with potassium iodide and starch paste. In the liquid condition, it is a powerful refrigerating agent. At very low temperatures, it forms with water a hydrate, $CH_3Cl.9H_2O$. It should not react alkaline to litmus (*ammonia and methylated ammonia—methylamine*). It should not immediately form a precipitate with silver nitrate. On evaporating it should leave no residue and emit no odor of methylamine.

Anesthetics, Local

There are three general groups of drugs used for the production of local anesthesia: (1) those which cause anesthesia through the production of cold, such as ether, ethyl chloride and methyl chloride; (2) certain protoplasmic poisons, as quinine; and (3) those having a specific effect on sensory nerves or their endings; cocaine is the type of this class.

The drugs listed below belong, in general, to the third class. They have been introduced with the object of finding substances less toxic and more stable and less injurious to the tissues than cocaine. Their anesthetic power is also as a rule somewhat less than that of cocaine and most of them present the usually undesirable effect of dilating the blood vessels or at least of not constricting them as does cocaine; and are therefore almost always employed in conjunction with epinephrine. The most important are based on the discovery that the local anesthetic action of cocaine is due to the radical of benzoic acid in combination with a nitrogen-containing basic group. The simplest of these compounds, ethylaminobenzoate (benzocaine, anesthesine), is the ethyl ester of paraaminobenzoic acid, $C_6H_4(NH_2)COOH$; orthoform is the methyl ester of oxyaminobenzoic acid, $NH_2C_6H_3(OH)COOH$. These are too weak or too slightly soluble in water to be useful for hypodermic injections; they are used as local applications (See "Anesthetics, Local, Slightly Soluble"). Procaine hydrochloride is the hydrochloride of a compound of paraaminobenzoic acid with diethylaminoethyl alcohol; its salts are readily soluble in water. Alypin is the hydrochloride of an ester produced by combination of benzoic acid with a derivative of an aminoamyl alcohol; it is very soluble in water, but it is much more toxic than the preceding compounds.

ALYPIN.—The hydrochloride of 2-benzoxy-2-dimethylaminomethyl-1-dimethylaminobutane.—$CH_3.CH_2.C(C_6H_5COO)[CH_2N(CH_3)_2].CH_2N:(CH_3)_2.HCl$.

Actions and Uses.—Alypin is a local anesthetic, claimed to be equal to cocaine, but is not a mydriatic. It is said not to produce disturbance of accommodation and to be less toxic than cocaine, but the evidence as to the relative toxicity of alypin and cocaine is rather conflicting. Death was reported in one case from the injection of about 7.4 cc. of a 10 per cent solution into the urethra and bladder; severe poisoning has resulted from smaller amounts.

Dosage.—Alypin is used in solutions the strength of which is about the same as that of cocaine hydrochloride. In ophthalmology, 2 to 4 per cent; in rhino-laryngology, 5 to 10 per cent; in urology, 1 to 4 per cent; in minor surgery, ½ to 2 per cent; in dentistry, 2 per cent.

Alypin solutions may be sterilized by boiling the required amount of water for 10 minutes in a test-tube stoppered with cotton; the drug is then added and the boiling continued over a small flame for another minute. Solutions should be freshly prepared. Epinephrine preparations may be added when a vasoconstrictor effect is desired.

Manufactured by The Bayer Co., Rensselaer, N. Y. (Winthrop Chemical Co., Inc., New York, distributor). U. S. patent 808,748 (Jan. 2, 1906; expired). U. S. trademark 44,608.

Alypin is a white, crystalline powder; odorless; bitter taste, hygroscopic. It is very soluble in water; freely soluble in alcohol and chloroform; insoluble in ether. Its aqueous solutions are neutral and are not rendered turbid on the addition of sodium bicarbonate solution in moderate quantities. Its aqueous solution may be sterilized by boiling for a period not exceeding five minutes without decomposition. Two and four per cent aqueous solutions are quite stable, but weaker solutions are likely to become moldy. It should be protected from the air in well stoppered containers. With the aqueous solution (1 in 100) potassium dichromate solution produces an orange-yellow, crystalline precipitate, which is soluble in hydrochloric acid. Potassium permanganate solution produces a violet crystalline precipitate, which turns brown on standing. The aqueous solution of alypin (1 in 100) gives precipitates with potassium mercuric iodide solution, iodine solution, picric acid solution, gold chloride solution and many other alkaloidal reagents; also it gives precipitates with potassium iodide solution and mercuric chloride solution. Mix 0.1 Gm. of alypin with 1 cc. of sulphuric acid, warm the mixture to 100 C. for five minutes and carefully add 2 cc. of water: the odor of ethylbenzoate is developed On cooling the mixture, crystals separate which are dissolved on adding 2 cc. of alcohol.

Dry about 1 Gm. of alypin, accurately weighed to constant weight at 100 C.: the loss should not exceed 2 per cent.

Incinerate about 0.5 Gm. of alypin, accurately weighed: the ash does not exceed 0.1 per cent.

APOTHESINE.—γ-diethylaminopropyl cinnamate hydrochloride. $(C_2H_5)_2N.CH_2.CH_2CH_2.COO.CH:CH.C_6H_5.HCl$. The hydrochloride of a condensation product prepared by the action of cinnamoyl chloride on γ-diethylaminopropylalcohol.

Action and Uses.—Apothesine is a local anesthetic of the procaine rather than the cocain type, that is, it belongs to that type which while effective for injection anesthesia (especially when combined with epinephrine), is relatively inefficient when applied to mucous membranes. It is rather slower in action than procaine. Its absolute toxicity is less than that of cocaine (as 20 to 15) but about twice that of procaine (as 20 is to 40). It is efficient and generally safe for injection. When injected, somewhat stronger solutions are required than are necessary with procaine, or especially with cocaine, but with adequate concentrations the anesthesia is just as complete. It is employed for infiltration injection, nerve blocking, intraspinal injection, pressure anesthesia, oral administration as a palliative measure for its local anesthetic effect, for post operative and persistent vomiting and pain of gastric ulcer Apothesine solutions are not injured by boiling.

Dosage.—As a local anesthetic 0.5 to 2 per cent solution generally with epinephrine in sterile water or physiologic solution of sodium chloride. For spinal anesthesia 2 cc. of a 4 per cent solution. For oral administration 0.03 Gm. repeated at half hour intervals.

Manufactured by Parke, Davis & Company, Detroit. U. S. patents 1,193,634; 1,193,649; 1,193,650 and 1,193,651 (Aug. 8, 1916; expires 1933).

Apothesine Solution: Each 100 cc. contains 1.5 Gm. of apothesine and 0.5 Gm. of chloretone (the latter is used as a preservative).

Apothesine Hypodermic Tablets 0.08 Gm. (1¼ Gr.).

Apothesine and Adrenalin Hypodermic Tablets: Each tablet contains apothesine 0.04 Gm. (⅗ grain) and adrenalin 0.00004 Gm. (1/1600 grain).

Apothesine and Adrenalin Hypodermic Tablets (℞ "B"); Each tablet contains apothesine 0.3 Gm. (5 grains) and adrenalin 0.0003 Gm. (1/200 grain).

Apothesine and Adrenalin Hypodermic Tablets Cylindrical (for pressure anesthesia): Each tablet contains apothesine 0.01 Gm. (⅙ grain) and adrenalin 0.000025 Gm. (1/2500 grain).

Apothesine Ointment: Contains apothesine 10 per cent, adrenalin 1: 60,000 and menthol 0.5 per cent. Supplied in 10 cc. collapsible tubes with elongated nozzle.

Apothesine occurs in white masses which are composed of small white crystals; practically odorless; faintly bitter, but producing a sense of numbness of the tongue; permanent in the air. It is soluble in water and alcohol; slightly soluble in acetone or ether. Its aqueous solution is neutral to litmus paper. The solution is stable. Aqueous solutions of apothesine produce precipitates with the alkaline hydroxides and their carbonates (the precipitate formed with sodium bicarbonate is soluble in an excess of the reagent) and with the usual alkaloidal reagents. The free base of apothesine occurs as an oil; when heated with strong sodium hydroxide, it is decomposed to diethylaminopropylalcohol and sodium cinnamate.

Apothesine melts at 136 C.

An aqueous solution of apothesine gives, with silver nitrate solution, a white precipitate which is insoluble in nitric acid.

Dissolve about 0.1 Gm. of apothesine in 5 cc. of water, add 2 drops of diluted hydrochloric acid and 2 drops of sodium nitrite solution (10 per cent) and mix with a solution of 0.2 Gm. of betanaphthol in 10 cc. of sodium hydroxide solution (10 per cent): A white precipitate is formed (distinction from *ethyl aminobenzoate,* which gives a cherry-red color in a solution containing undissolved benzocaine and from *procaine hydrochloride,* which gives a scarlet precipitate).

Add a few drops of gold chloride solution to an aqueous solution of apothesine (1 in 100): a lemon-yellow precipitate is produced (distinction from *ethyl aminobenzoate* and *procaine hydrochloride* which form brown precipitates).

Dissolve about 0.1 Gm. of apothesine in 5 cc. of water, add 3 drops of diluted sulphuric acid and 5 drops of potassium permanganate solution: the violet color of the latter disappears immediately (distinction from *cocaine* which gives a violet precipitate).

Dissolve 0.1 Gm. of apothesine in 1 cc. of sulphuric acid: the solution remains colorless (*organic impurities*).

Dissolve 0.1 Gm. of apothesine in 10 cc. of water and saturate the solution with hydrogen sulphide: no coloration or precipitation is produced (*salts of heavy metals*).

Incinerate about 0.5 Gm. of apothesine, accurately weighed: not more than 0.1 per cent. of residue remains.

BENZYL ALCOHOL.—Alcohol Benzylicum.—Phenmethylol.—$C_6H_5.CH_2OH$.—An aromatic alcohol occurring as an ester in tolu and other balsams; the product on the market is produced synthetically.

Actions and Uses.—Benzyl alcohol is used as a local anesthetic by injection and by application to mucous membranes. It is practically nonirritant and nontoxic in the ordinary concentrations and doses.

Dosage.—Benzyl alcohol is usually used in the form of a 1 to 4 per cent solution in water or physiological solution of sodium chloride. Such solutions may be sterilized by boiling, without danger of decomposition. Pure benzyl alcohol is markedly antiseptic. The technic of injection is the same as for other local anesthetics. It is applied against pruritis as a 10 per cent ointment, in lard; or as a lotion of equal parts of benzylalcohol, alcohol and water.

Benzyl alcohol is a colorless liquid with a faint aromatic odor, and a sharp burning taste. When placed on the tongue, it produces numbness, even if only a small quantity is used. It is soluble, 1 cc. in 25 cc. of water, and miscible in all proportions with alcohol, ether, and chloroform. One volume of benzyl alcohol should dissolve in 1.5 volumes of 50 per cent alcohol. Benzyl alcohol boils without decomposition between 200 and 206 C. When ignited it burns with a smoky flame. It has a specific gravity of from 1.040 to 1.050 at 15 C., and 1.032 to 1.042 at 25 C.

Benzyl alcohol is neutral to litmus. If 2 or 3 drops are added to a strong solution of potassium permanganate acidulated with sulphuric acid, rapid oxidation takes place and the odor of benzaldehyde is plainly evident. On heating the mixture, further oxidation takes place, and then by adding dilute sulphuric acid and decolorizing the mixture with hydrogen dioxide, benzoic acid may be obtained by extracting with ether. Wind the end of a copper wire to a spiral about 6.3 mm. (one-fourth inch) in diameter and length, hold this spiral in a nonluminous flame until no green coloration is imparted to the flame: dip the spiral into the benzyl alcohol to be tested and burn off the adhering liquid outside the flame: place the nonluminous flame against a dark background and hold the loop in the right or left margin of the flame: not even a transient green coloration should be imparted to the latter (*limit of chlorine compounds*). If 5 cc. is shaken with 5 cc. of sodium hydroxide solution (5 per cent) and allowed to stand one hour, no yellow color should appear in the aqueous layer (*aldehyde*).

Ten cc. of benzyl alcohol should leave no weighable residue on evaporation and heating until all carbon is burned away.

Benzyl Alcohol-Seydel.—A brand of benzyl alcohol-N. N. R.

Manufactured by The Seydel Chemical Company, Jersey City, N. J. No U. S. patent or trademark.

Phenmethylol-H. W. & D.—A brand of benzyl alcohol-N. N. R.

Manufactured by Hynson, Westcott & Dunning, Baltimore, Md. No U. S. patent or trademark.

Phenmethylol Ampules, 1 per cent.-H. W. & D.: ampules containing 5 cc. of a sterile solution of phenmethylol-H. W. & D. 1 Gm., in physiological solution of sodium chloride, 99 Gm.

Phenmethylol Ampules, 2 per cent.-H. W. & D.: ampules containing 5 cc. of a sterile solution of phenmethylol-H. W. & D. 2 Gm., in physiological solution of sodium chloride, 98 Gm.

Phenmethylol Ampules, 4 per cent.-H. W. & D.: ampules containing 5 cc. of a sterile solution of phenmethylol-H. W. & D. 4 Gm., in physiological solution of sodium chloride, 96 Gm.

BUTYN. — *p*-Aminobenzoyl-γ-dinormalbutylaminopropanol sulphate.—γ-dibutylaminopropyl-*p*-aminobenzoate-*N*-sulphate. —$[NH_2.C_6H_4.COO(CH_2)_3.N(C_4H_9)_2]_2.H_2SO_4$. Butyn is the normal sulphate of a base resembling the base of procaine hydrochloride *p*-aminobenzoyl-diethylaminoethanol); but it differs in that butyn possesses a butyl group in place of the ethyl group of procaine base, and a propanol group in place of the ethanol group.

Actions and Uses.—Butyn is a local anesthetic proposed as a substitute for cocaine, particularly in surface anesthesia, as for the eye, nose and throat. It has the special advantage of acting through intact mucosae almost as effectively as cocaine. On the normal human eye, a 1 per cent solution of butyn is as effective as a 1 per cent solution of phenacaine (holocaine), and more efficient than a 1 per cent solution of cocaine or a 1 per cent solution of eucaine. Butyn solutions are nonirritant.

When injected hypodermically into albino rats, the toxicity of butyn is two and one-half times that of cocaine; but the lethal dose (injected intravenously into cats) is about equal to that of cocaine. Pharmacologic study indicates that butyn may take the place of cocaine, in whole or in part, for surface anesthesia of mucous membranes and that it may be superior for this purpose, especially for use in the eye, to other anesthetics, for the reason that it can be used in materially lower concentrations (presumably because of more prompt absorption). On the other hand, it does not appear promising for injection anesthesia or for spinal anesthesia, since its toxicity is materially greater than that of procaine hydrochloride; but butyn is used for injection anesthesia, in concentrations of 0.1 to 0.4 per cent.

A committee of the Section on Ophthalmology of the American Medical Association (*J. A. M. A.* **78**:343 [Feb. 4] 1922) reported the successful use of butyn in practically all operations on the eye and in some operations on the nose and throat. The committee concluded that butyn is more powerful than cocaine, a smaller quantity being required; that it acts more rapidly than cocaine, and that the action is more prolonged. So far as the experiences of the committee go, butyn in the quantity required is less toxic than cocaine. The committee found butyn superior to cocaine in that it produces no drying of the tissues and no change in the size of the pupil and that it has no ischemic effect.

Dosage.—For ophthalmologic work, butyn is generally used in 2 per cent solutions. A single application produces, within one minute, an anesthesia sufficient to permit the removal of superficially placed foreign bodies, the application of irritant astringents and the use of the tonometer. Four instillations, three minutes apart, permit operative work within five minutes after the last instillation, producing an anesthesia sufficient to perform all of the commoner operations on the eye. For topical use in nose and throat work, a 2 per cent solution is usually employed. Butyn solutions may be sterilized by boiling.

Manufactured by The Abbott Laboratories, North Chicago. U. S. patent 1,358,751 (Nov. 16, 1920; expires 1937). U. S. trademark 147,893.

Butyn Solution, 2 per cent.

Butyn Tablets, 0.2 Gm. (3 grains).

Butyn and Epinephrin Hypodermic Tablets: Butyn 0.01 Gm. (1/6 grain), epinephrin-Abbott, 0.032 mg. (1/2000 grain).

Butyn is a colorless, odorless solid which rapidly produces a sense of numbness when placed upon the tongue.

It melts at from 98 to 100 C.

Butyn is soluble in less than its own weight of water at 20 C. It dissolves slowly in cold water, but rapidly in hot water. It is very

soluble in warm alcohol and in acetone, from which it does not readily separate on cooling. It is slightly soluble in chloroform, and insoluble in ether.

From aqueous solutions of butyn, alkali hydroxides and carbonates, precipitate the free base as a colorless oil: the soluble bicarbonates precepitate a crystalline butyn carbonate. When the separated base is exactly neutralized with hydrochloric acid, the white hydrochloride crystallizes out; after drying at 100 C., these crystals melt at 151 C.

Dissolve one gram of butyn in 10 cc. of water: separate portions of the solution yield a white precipitate with potassium mercuric iodide solution; a brown precipitate with iodine solution; a brown precipitate with gold chloride solution; and a yellow precipitate with picric acid solution; a portion to which barium chloride solution is added gives a white precipitate (*distinction from procaine hydrochloride*).

Dissolve about 0.1 Gm. of butyn in 5 cc. of water, add 2 drops of diluted hydrochloric acid and 2 drops of sodium nitrite solution (10 per cent) and mix with a solution of 0.2 Gm. of betanaphthol in 10 cc. of sodium hydroxide solution (10 per cent); a scarlet red precipitate is formed (*distinction from phenacaine, which gives a white precipitate*).

To a solution of about 0.1 Gm. of butyn in 5 cc. of water, add 3 drops of diluted sulphuric acid and mix with 5 drops of potassium permanganate solution: the violet color of the latter disappears immediately (*distinction from cocaine*).

Dissolve about 0.1 Gm. of butyn in 1 cc. of sulphuric acid: the solution is colorless (*organic impurities*).

Dissolve 0.1 Gm. of the salt in 10 cc. of water and saturate with hydrogen sulphide: no coloration or precipitation occurs (*salts of heavy metals*).

Incinerate about 0.5 Gm. of butyn, accurately weighed: there is not more than 0.2 per cent residue.

Butyn Ointment-M. E. S. Co.: Butyn, 1 per cent; water, 1 per cent; wool fat and petrolatum, 98 per cent. Put up in collapsible tubes for application to the eye.

Prepared by Manhattan Eye Salve Co., Louisville, Ky.

PHENACAINE.—Phenacaina.—Holocaine Hydrochloride.—Ethenyl-*p*-diethoxydiphenylamidine Hydrochloride. — $CH_3C:-(NC_6H_4OC_2H_5).(NH.C_6H_4OC_2H_5).HCl+H_2O$.—The hydrochloride of phenetidylacetphenetidin, a basic condensation product of paraphenetidin (*p*-ethoxyaminobenzene) and acetparaphenetidin. Phenacaine was first introduced as holocaine hydrochloride.

Actions and Uses.—Phenacaine is a local anesthetic like cocaine but having the advantage of a quicker effect. Five minims of a 1 per cent solution when instilled into the eye are usually sufficient to cause anesthesia in from one to ten minutes. This is preceded by temporary smarting.

Dosage.—It is applied in a 1 per cent aqueous solution. Phenacaine is incompatible with alkalis and their carbonates and the usual alkaloidal reagents. Glass vessels should be avoided in preparing the solution, porcelain being used instead. The solutions are permanent, as the drug is itself antiseptic. They are not injured by boiling.

Holocaine Ointment-M. E. S. Co.: holocaine, 1 per cent; water, 1 per cent; wool fat and petrolatum, 98 per cent. Put up in collapsible tubes, for application to the eye.

Prepared by Manhattan Eye Salve Co., Louisville, Ky.

Holocaine and Adrenalin Ointment-M. E. S. Co.: composed of holocaine, 1 per cent; adrenalin chloride, 4 per cent; wool fat, 10 per cent;

white petrolatum, 85 per cent. Put up in collapsible tubes, for application to the eye.

Prepared by Manhattan Eye Salve Co., Louisville, Ky.

Phenacaine forms small, colorless crystals; odorless; faintly bitter and producing transient numbness on the tongue; permanent in the air.

Phenacaine is soluble in about 50 parts of water; freely soluble in alcohol and in chloroform; insoluble in ether. On boiling in glass vessels, the aqueous solution becomes turbid owing to a separation of a small quantity of the free base by the alkali derived from the glass. Phenacaine forms a clear, colorless solution in water, the solution having a neutral or faintly alkaline reaction on litmus.

The aqueous solution of phenacaine yields a white precipitate on the addition of silver nitrate solution or of ammonia water. The addition of a few drops of solution of chlorinated soda to a saturated, aqueous solution of phenacaine produces a finely divided, flesh-colored precipitate. In a few minutes, this separates as a violet-colored precipitate, and if the mixture is shaken with ether, the ether is colored Burgundy red. Dissolve about 0.05 Gm. of phenacaine in 2 cc. of concentrated hydrochloric acid, boil for two or three minutes, cool and add one drop of potassium dichromate solution: no ruby-red precipitate is produced (*absence of 5 per cent or more of acetphenetidin or paraphenetidin*).

Dry about 1 Gm. of phenacaine, accurately weighed, to constant weight at from 100 to 105 C.: the loss does not exceed 7 per cent.

Phenacaine dried as above melts at 189 C.

To about 25 cc. of water add 5 cc. of ammonia water contained in a separator, add about 0.5 Gm. of phenacaine, accurately weighed, which has been previously dried to constant weight at from 100 to 105 C. Extract the free base by shaking with successive portions of chloroform. (Preserve the solution in the separator for the test for phosphorous compounds given below.) Collect the chloroform solutions in a beaker by passing them through a small funnel holding a pledget of cotton. Evaporate the chloroform and dry the free base at from 100 to 105 C. to constant weight: the weight obtained should be not less than 87.5 or more than 90.5 per cent of the weight taken.

Purify the base by crystallization from hot alcohol, and after drying to constant weight, determine the melting point: it melts at from 116 to 117 C.

To the solution remaining in the separator, after the original extraction of the base, add an equal volume of nitric acid and boil for five minutes. Evaporate this solution to about 25 cc. and add to it 25 cc. of ammonium molybdate solution. Keep the mixture at a temperature of about 60 C. for three hours: no yellow precipitate is produced (*phosphorus compounds*).

Incinerate about 0.5 Gm. of phenacaine accurately weighed: not more than 0.1 per cent. of ash remains.

Holocaine.—A brand of phenacaine-N. N. R.

Manufactured by H. A. Metz Laboratories, Inc., New York. No U. S. patent.

Phenacaine-Werner.—A brand of phenacaine-N. N. R.

Manufactured by the Werner Drug and Chemical Company, Cincinnati, Ohio. No U. S. patent or trademark.

PROCAINE HYDROCHLORIDE.—For description see the U. S. Pharmacopeia under Procainae Hydrochloridum.

Actions and Uses.—Procaine hydrochloride is a local anesthetic similar in action to cocaine, but less toxic than cocaine and most other cocaine substitutes. When injected subcutaneously it exerts a prompt and powerful anesthetic action, but the effect is not sustained. This may be remedied by the simultaneous injection of epinephrine. Procaine hydrochloride is nonirritant. (See note under Creosote and Guaiacol Compounds.)

It is relatively ineffective when applied to intact mucous membranes.

Dosage.—For infiltration anesthesia, solutions of 0.25 Gm. (4 grains) procaine hydrochloride in 100 or 50 cc. (3.2 or 1.6 ounces) physiological solution of sodium chloride, with 0.3 or 0.6 cc. (5 or 10 minims) of epinephrine solution (1 in 1,000); for instillations and injections, solutions of 0.1 Gm. (1½ grains) procaine hydrochloride in 10 or 5 cc. (160 or 80 minims) physiological solution of sodium chloride, with or without 0.6 cc. (10 minims) of epinephrine solution (1 in 1,000). In ophthalmology, 1 to 5 or even up to 10 per cent solution, in rhinolaryngology, 5 to 20 per cent solutions are recommended, with the addition of 0.4 to 0.5 cc. (6 to 8 minims) of epinephrine solution (1 in 1,000) to each 10 cc. (160 minims). Internally, owing to its feeble toxicity, it may be given in doses up to 0.5 Gm. (8 grains) to adults.

Novocain.—A brand of procaine hydrochloride-U. S. P.

Manufactured by H. A. Metz Laboratories, Inc., New York, under U. S. patent 812,554 (Feb. 13, 1906; expired) by license of the U. S. Federal Trade Commission. U. S. trademark 53,072.

Novocain Hypodermic Tablets "D": Each tablet contains novocain 0.2 Gm. (3 grains).

Novocain Hypodermic Tablets "F": Novocain 0.05 Gm. (⅚ grain).

Novocain Hypodermic Tablets "T": Novocain 0.02 Gm. (⅓ grain) and l-suprarenin synthetic 0.00002 Gm. (1/3000 grain).

Novocain and L-Suprarenin Synthetic Hypodermic Tablets "A": Novocain 0.125 Gm. (2 grains) and l-suprarenin synthetic 0.000125 Gm. (1/500 grain).

Novocain and L-Suprarenin Synthetic Hypodermic Tablets "B": Novocain 0.1 Gm. (1½ grains) and l-suprarenin synthetic 0.00025 Gm. (1/250 grain).

Novocain and L-Suprarenin Synthetic Hypodermic Tablets "C": Novocain 0.05 Gm. (⅚ grain) and l-suprarenin synthetic 0.000083 Gm. (1/780 grain).

Novocain and L-Suprarenin Synthetic Hypodermic Tablets "E": Novocain 0.02 Gm. (⅓ grain) and l-suprarenin synthetic 0.00005 Gm. (1/1200 grain).

Novocain and L-Suprarenin Synthetic Hypodermic Tablets "H": Each contains novocain, 0.06 Gm. (1 grain), and l-suprarenin synthetic, 0.00006 Gm. (1/1000 grain).

Novocain Solution 1 Per Cent Ampules: Each contains novocain, 0.06 Gm. (1 grain), sodium chloride, 0.036 Gm. (½ grain) and distilled water, 6 cc. (90 minims).

Procaine-Abbott.—A brand of procaine hydrochloride-U. S. P.

Manufactured by The Abbott Laboratories, North Chicago. U. S. patent 812,554 (Feb. 13, 1906; expired).

U. S. patent 1,260,289 (March 26, 1918; expires 1935).

Procaine-Epinephrin Ampules 1 Cc.—Procaine-Abbott 0.02 Gm. (⅓ grain), epinephrine 0.00004 Gm. (1/1600 grain) in Ringer solution 1 cc.

Procaine Hypodermic Tablets, ¾ grain.

Procaine-Epinephrin Hypodermic Tablets, No. 1: Each contains procaine-Abbott 0.02 Gm. (⅓ grain), epinephrine chloride 0.00002 Gm.

(1/2500 grain) and sufficient sodium chloride to cause the resulting solution to be isotonic when the tablet is dissolved in 1 cc. of water.

Procaine-Epinephrin Hypodermic Tablets No. 2: Procaine-Abbott 0.02 Gm. (1/3 grain), epinephrine 0.00004 Gm. (1/1500 grain) and sodium chloride sufficient so that when the tablet is dissolved in 1 cc. of water, the resulting solution is isotonic.

PROCAINE NITRATE.—Procainae Nitras.—$C_6H_4.NH_2CO O.C_2H_4.N(C_2H_5)_2.HNO_3$. — 1-*p*-aminobenzoyl-2-diethylaminoethanol mononitrate; *p*-aminobenzoxydiethylaminoethane mononitrate; β-diethylaminoethyl-*p*-amino benzoate mononitrate.

Actions and Uses.—The same as those of procaine hydrochloride. It may be prescribed in combination with silver salts, with which it forms no precipitate.

Dosage.—Used in 3 per cent solutions.

Procaine nitrate occurs in small colorless and odorless crystals, soluble in water and alcohol. The aqueous solution is neutral in reaction. Melting-point 100 to 102 C.

If 0.1 Gm. procaine nitrate is dissolved in 1 cc. concentrated sulphuric acid and a solution of ferrous sulphate carefully floated above it, a brown zone is formed at the surface of contact of the two solutions. One part of procaine nitrate dissolved in 10 parts of water and acidified with nitric acid should yield no precipitate on the addition of silver nitrate solution. It also yields the general tests described under procaine hydrochloride.

TUTOCAIN. — Butamin. — *p*-amino-benzoyldimethylaminomethyl-butanol hydrochloride.—γ-dimethylamino-α, β-dimethylpropyl-*p*-aminobenzoate hydrochloride. — *p*-aminobenzoyl-dimethylamino 1:2 dimethyl-propanol hydrochloride.—$(CH_3)_2 N.CH_2.CH(CH_3)CH(CH_3)(O.CO.C_6H_4.NH_2)HCl$.—The base of tutocain belongs to the procaine type, but in addition possesses two asymmetric carbon atoms; it is optically inactive. Tutocain is therefore a racemic mixture of the hydrochlorides.

Actions and Uses.—Tutocain is used by subcutaneous injection, but more especially for surface anesthesia. When correctly used, tutocain rapidly produces complete and prolonged anesthesia and is effective even in relatively low concentration.

It is reported that complete anesthesia of the cornea occurs four minutes after the application of 0.25 to 1 per cent solutions of tutocain; surface anesthesia in the nose, throat and eyes is reported to develop more slowly than with cocaine, but to be equally intense. When tutocain is used by injection, the effects are very prompt.

In wheal tests on human beings, a 1 per cent tutocain solution produced an anesthesia that lasted for from fifteen to twenty minutes; one-eighth per cent solution containing epinephrine gave an anesthesia that lasted for about two hours. In experiments made for the Council, tutocain in 3 per cent solution is about four times as toxic as procaine hydrochloride by rapid intravenous injection into the cat and a fatality has been reported following the injection of 8 cc. of a 2 per cent solution into the urethra. On the other hand, experiments and clinical trials have been reported in support of the claim that tutocain is relatively safe for use in surface anesthesia and by hypodermic injection.

Dosage.—For application to the eye, nose and throat, 2 to 5 per cent solutions of tutocain are used; for applications to the urethra, 0.5 to 1 per cent solutions, increased to 2 per cent in very painful procedures; for infiltration anesthesia, 0.2 per cent solutions are generally used.

Tutocain solutions may be sterilized by boiling for a short time.

Manufactured by The Bayer Company, Inc., Rensselaer, N. Y. (Winthrop Chemical Co., Inc., New York, distributor). U. S. patent 1,474,567 (Nov. 20, 1923; expires 1940). U. S. trademark 180,610.

Tablets Tutocain No. 1 (with Suprarenin): Each tablet contains tutocain, 0.03 Gm.; epinephrine, 0.00015 Gm.

Tablets Tutocain No. 2 (with Suprarenin): Each tablet contains tutocain, 0.03 Gm.; epinephrine, 0.00006 Gm.

Tablets Tutocain No. 3: Each tablet contains tutocain, 0.03 Gm.

Tablets Tutocain No. 4 (with Suprarenin): Each tablet contains tutocain, 0.05 Gm.; epinephrine, 0.000125 Gm.

Tablets Tutocain No. 5: Each tablet contains tutocain 0.1 Gm.

Tablets Tutocain No. 6: Each tablet contains tutocain 0.05 Gm.

Tutocain occurs as a light, ivory colored crystalline powder; practically odorless; when applied on the tongue, it possesses a faintly bitter taste followed by a sense of numbness; permanent in the air; easily soluble in water (about 1 in 4); difficultly soluble in alcohol (1 in 50). Its aqueous solution (1 in 10) is neutral to litmus paper. It is optically inactive. It melts at 212 to 215 C. From aqueous solutions, alkali hydroxides and carbonates precipitate the free base as a light yellowish oil which solidifies after some time and melts at not less than 81 C.

Dissolve about 0.1 Gm. in 5 cc. of water, add 2 drops of diluted hydrochloric acid and 2 drops of sodium nitrite solution (10 per cent) and mix with a solution of 0.2 Gm. of betanaphthol in 10 cc. of sodium hydroxide solution (10 per cent): a scarlet red precipitate is formed (*distinction from phenacaine,* which gives a white precipitate). Dissolve 1 Gm. in 10 cc. water: to separate portions of 2 cc. each, the solutions yield a white precipitate with 1 cc. of potassium mercuric iodide solution; a brown precipitate with 1 cc. of iodine solution; a brown precipitate with 1 cc. of gold chloride solution (*distinction from apothesine,* which gives a lemon yellow precipitate); a yellow precipitate with 1 cc. of picric acid solution; a white curdy precipitate with 1 cc. of nitric acid and 1 cc. of silver nitrate solution. Dissolve 0.1 Gm. in 5 cc. water add 2 drops diluted hydrochloric acid and 1 cc. barium chloride solution: no precipitate forms (*distinction from butyn*). To a solution of about 0.1 Gm. in 5 cc. of water, add 3 drops of diluted sulphuric acid and mix with 5 drops of potassium permanganate solution: the violet color of the latter disappears immediately (*distinction from cocaine*). Dissolve about 0.1 Gm. in 1 cc. of sulphuric acid: the solution is colorless (*organic impurities*). Dissolve 0.1 Gm. in 10 cc. water and saturate with hydrogen sulphide: no coloration or precipitation occurs (*salts of heavy metals*).

Dry about 1 Gm. accurately weighed to constant weight at 100 C.: the loss does not exceed 1 per cent. Incinerate about 0.5 Gm. accurately weighed: there is not more than 0.2 per cent residue.

Dissolve about 1 Gm. previously dried to constant weight at 100 C., weigh accurately and add a few pieces of ice, 15 cc. of hydrochloric acid and titrate with tenth-normal sodium nitrite solution using starch iodide paper as an indicator: the amount of tenth-normal sodium nitrite consumed corresponds to not less than 99 per cent nor more than 101 per cent.

Anesthetics, Local, Slightly Soluble

The slight solubility of these anesthetics renders them unsuitable for injection, but the slow absorption renders them safer, especially for ulcers, wounds, and mucous surfaces. The anesthesia which they induce is usually not so complete as that induced by the soluble local anesthetics; but it is more lasting. As a group they are practically nonirritant and nontoxic. Ethyl Aminobenzoate (Benzocaine, Anesthesin) and orthoform are about equally effective through intact mucous membranes; butesin is claimed to be more effective than Ethyl Aminobenzoate.

They are used for painful wounds, ulcers, etc., of the skin and accessible mucous membranes; for instance, after dental operations. They have all been used to relieve or control the pain of gastric ulcer or cancer and other gastralgias, but here their efficiency is doubtful.

ETHYL AMINOBENZOATE.—For description see the U. S. Pharmacopeia under Aethylis Aminobenzoas.

Actions and Uses.—See preceding article, Anesthetics, Local, Slightly Soluble.

Dosage.—Internally, from 0.3 to 0.5 Gm. (5 to 8 grains). Externally, it is applied as a dusting powder, either pure or diluted. It may be applied in ointment or in the form of suppositories.

Anaesthesine.—A brand of Ethyl Aminobenzoate-U. S. P.

Manufactured by H. A. Metz Laboratories, Inc., New York. No U. S. patent. U. S. trademark 55,744 (Anästhesin).

Anesthesin-Abbott.—A brand of Ethyl Aminobenzoate-U. S. P.

Manufactured by The Abbott Laboratories, North Chicago. No U. S. patent. U. S. trademark 55,744 (Anästhesin).

BUTESIN. — *n*-butyl-*p*-aminobenzoate. — $C_6H_4NH_2.COO(C_4H_9)$. — The normal butyl ester of 4-aminobenzoic acid, $C_6H_4NH_2.COOH$.

Actions and Uses.—See preceding article, Anesthetics, Local, Slightly Soluble. The actions and uses of butesin are similar to those of Ethyl Aminobenzoate-U. S. P., but it is claimed to be more effective.

Dosage.—Butesin is used as a dusting powder, either pure or diluted. It may be used in the form of troches, ointment, or suppositories or dissolved in a fatty oil. Its oil solutions may be sterilized by heat.

Manufactured by The Abbott Laboratories, North Chicago. U. S. patent 1,440,652 (issued Jan. 2, 1923; expires 1940). U. S. trademark applied for.

Butesin is a white, crystalline powder, odorless and tasteless. It is almost insoluble in water (about 1 in 7,000); soluble in dilute acids, alcohol, chloroform, ether and benzene; also soluble in fatty oils. Butesin is slowly hydrolysed when boiled with water. It melts at 56 to 57 C. and boils at 147 C. under 2 mm. pressure. Butesin yields colorless solutions in alcohol and ether. The addition of silver nitrate solution to its alcoholic solution acidified with nitric acid produces no precipitate. A solution of butesin in diluted hydrochloric acid is not affected by saturation with hydrogen sulphide.

Add a few drops of sodium nitrite solution (1 in 10) to 2 cc. of a solution of butesin (1 in 100) in very dilute hydrochloric acid and mix with 0.2 Gm. of betanaphthol in 10 cc. of sodium hydroxide solution (10 per cent): a scarlet red precipitate is given at once. To about 1 cc. of a solution of butesin (1 in 100) in very dilute hydrochloric acid, add a few drops of iodine solution, shake the mixture and allow to stand for 10 minutes with occasional agitation: a dark brown precipitate is formed which changes into large, reddish-brown prisms (*distinction from ethyl aminobenzoate which gives lustrous scales*).

BUTESIN PICRATE. — Dinormalbutyl-*p*-aminobenzoate-trinitrophenol. $(C_6H_4.NH_2.COO.C_4H_9)_2.C_6H_2(NO_2)_3OH$.—Compound consisting of one molecule of trinitrophenol (picric acid) and two molecules of the normal butyl ester of 4-amino benzoic acid.

Actions and Uses.—Butesin picrate combines the anesthetic action of butesin with the antiseptic properties of trinitrophenol (picric acid). An aqueous solution of 1 in 2,000 produces immediate and complete anesthesia of the eye which lasts from ten to twenty minutes. Butesin picrate is used in the treatment of burns, ulcers and other denuded painful lesions of the skin.

Dosage.—For use, a 1 per cent butesin picrate ointment is proposed.

Manufactured by The Abbott Laboratories, North Chicago. U. S. patent 1,596,259 (Aug. 17, 1926; expires 1943). U. S. trademark applied for.

Butesin Picrate Dusting Powder: Butesin picrate, 5 per cent; sodium stearate, 95 per cent.

Butesin Picrate Ointment: Butesin picrate 1 part, incorporated in an ointment base composed of white wax, paraffin, liquid petrolatum, water and sodium borate 0.5 per cent, 99 parts.

Butesin picrate is a yellow, amorphous powder; odorless; taste slightly bitttr. One part of buttsin picrate is soluble in 2,000 parts of water; also soluble in 100 parts of cottonseed oil; soluble in alcohol, chloroform, ether and benzene. It melts at 109 to 110 C.

The aqueous solution of butesin pictrate is greenish yellow; the color is intensified by the addition of alkali and is decreased by acid. A saturated, aqueous solution of butesin picrate is not affected by the addition of mercuric potassium iodide solution, by silver nitrate solution or by hydrogen sulphide solution. A few drops of sodium nitrite solution added to the acidulated solution of butesin picrate followed by a few drops of a slightly alkaline solution of betanaphthol produces a salmon-colored precipitate which quickly darkens. A purplish red color is produced if a one per cent potassium cyanide solution be added to an aqueous solution of butesin picrate.

Incinerate 0.5 Gm. of butesin picrate, accurately weighed: the ash does not exceed 0.1 per cent.

ORTHOFORM. — Orthoform-New. — Methyl m-amino-*p*-oxybenzoate. — $C_6H_3.NH_2.OH.CO.O.(CH_3)$, 3:4:1. — The m-amino-*p*-oxybenzoic acid ester of methyl alcohol.

Actions and Uses.—Orthoform is a local anesthetic, but penetrates the tissues very slowly on account of its insolubility. It has no action on the unbroken skin. It is practically nontoxic in the usual doses.

Orthoform is used internally to relieve the pain of gastric ulcer. It has been applied locally as an analgesic to wounds of every description. It has been used in dentistry, in nasal catarrh, hay-fever, etc.

Dosage.—Internally, from 0.5 to 1 Gm. (8 to 15 grains) in emulsion; locally, in substance as a dusting-powder or mixed with milk sugar for insufflation, dissolved in ether and mixed with oil for pencilings, or as an ointment with wool fat, etc.

Manufactured by H. A. Metz Laboratories, Inc., New York. U. S. patent 610,348 (Sept. 6, 1898; expired), and 625,158 (May 16, 1899; expired).

Orthoform occurs in a fine, white, crystalline powder, neutral in reaction, and melting at from 141 to 143 C., odorless and tasteless. It is almost insoluble in water; freely soluble in alcohol; soluble in ether. It is decomposed by boiling with water or by warming with alkalies or their carbonates, into methyl alcohol and paraoxybenzoic acid or the alkali salt of it. When crystallized from chloroform it sometimes assumes the form of white crystals, melting at from 110 to 111 C., returning on melting to the ordinary form.

The filtrate obtained after shaking a small quantity of the orthoform with water produces a fugitive color with ferric chloride and should not give a reaction with silver nitrate. A solution of 0.1 Gm. orthoform dissolved in 2 cc. of water by the aid of hydrochloric acid is colered yellowish red on addition of sodium nitrite and then deposits a yellow precipitate, deepening to red on exposure to the air.

ANTIMONY COMPOUNDS

ANTIMONY THIOGLYCOLLAMIDE.—The triamide of antimony thioglycollic acid $Sb(S.CH_2CO.NH_2)_3$. It contains not less than 30 per cent of antimony.

Actions and Uses.—Antimony thioglycollamide and antimony sodium thioglycollate have been tested on rats, rabbits and dogs inoculated with trypanosomes by Rowntree and Abel (*J. Pharmacol. & Exper. Therap.* **2**:101, 1910). The findings were so favorable that these workers suggested the employment of these antimony compounds in the treatment of human trypanosomiasis and in trypanosomic diseases of the larger animals. Randall has used both of these antimony compounds intravenously and intramuscularly in granuloma inguinale (*J. Urol.* **9**:491, 1923, and *Am. J. M. Sc.* **168**:728, 1924) with marked success. In the doses employed they were less toxic and less irritating than tartar emetic and the results obtained were decidedly more favorable. From the results obtained by Rowntree and Abel and by Randall as mentioned above, the experimental use of these antimony compounds in kala azar and filiariasis would appear justifiable.

Dosage.—The usual intramuscular or intravenous dose employed by Randall is 0.08 Gm., dissolved in 20 cc. of sterile water every second day until from 15 to 25 injections had been given. He recommends that at least 12 injections be given after the first healing has taken place to insure permanent cure. Its solutions are incompatible with solutions of the fixed alkalis.

Manufactured by Hynson, Westcott and Dunning, Baltimore. No U. S. patent or trademark.

Ampules Solution Antimony Thioglycollamide, 0.4 per cent, 20 cc.

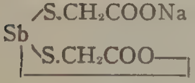
Antimony thioglycollamide is a white, crystalline, odorless powder. It is soluble in about 200 parts of water; somewhat soluble in alcohol; insoluble in ether. It melts at about 139 C. (uncorrected).

Dissolve a few crystals of antimony thioglycollamide in 5 cc. of water and add a drop of ferric chloride solution: a transient blue color appears. Boil about 0.1 Gm. of antimony thioglycollamide with 5 cc. of sodium hydroxide solution: ammonia is evolved. Dissolve about 0.1 Gm. of antimony thioglycollamide in 25 cc. of warm water, add a few drops of diluted hydrochloric acid and pass in hydrogen sulphide: an orange precipitate is produced.

Dissolve 0.2 Gm. of antimony thioglycollamide in 5 cc. of hydrochloric acid, add 10 cc. of freshly prepared stannous chloride solution and allow to stand 30 minutes: no brownish tint or precipitate is visible if viewed from above over a white surface (*arsenic*). A blank test should be carried out, using the same quantities of reagents.

Weigh accurately from 0.2 to 0.3 Gm. of antimony thioglycollamide, dissolve it in about 100 cc. of warm water, add 1 cc. of diluted hydrochloric acid, pass in hydrogen sulphide until precipitation is complete and allow to stand 30 minutes. Collect the antimony sulphide in a weighed Gooch crucible, wash it successively with water containing hydrogen sulphide, alcohol, ether, carbon disulphide, alcohol and ether, dry the residue at 110 C. and weigh. The antimony sulphide obtained corresponds to not less than 30 per cent of antimony.

ANTIMONY SODIUM THIOGLYCOLLATE.—The compound formed by dissolving antimony trioxide in a solution of a mixture of sodium thioglycollate and thioglycollic acid.



$$\mathrm{Sb}\begin{cases}\mathrm{S.CH_2COONa}\\ \mathrm{S.CH_2COO}-\end{cases}$$

It contains not less than 37 per cent of antimony.

Actions and Uses.—The same as antimony thioglycollamide. It is more soluble than antimony thioglycollamide, and in higher dosages it appears to be less toxic.

Dosage.—From 0.05 to 0.1 Gm. (1 to 2 grains) dissolved in 10 to 20 cc. of sterile water every third or fourth day until from 15 to 25 injections have been given. Its solutions are incompatible with solutions of the fixed alkalis.

Manufactured by Hynson, Westcott and Dunning, Baltimore. No U. S. patent or trademark.

Ampules Solution Antimony Sodium Thioglycollate, 0.5 per cent, 20 cc.

Antimony sodium thioglycollate is a white or faintly pinkish powder; odorless or having a faint odor of mercaptan; very soluble in water; insoluble in alcohol.

Add a drop of diluted hydrochloric acid to 3 cc. of a dilute solution of antimony sodium thioglycollate (1 in 100) and add two drops of 1 per cent ferric chloride solution: a transient blue color results. Add a drop of 1 per cent ammonia water to this mixture and shake: a Burgundy red color results. Add a few drops of sodium hydroxide solution to a dilute solution of antimony sodium thioglycollate (1 in 100):

a white precipitate is produced. Dissolve about 0.1 Gm. of antimony sodium thioglycollate in 2 cc. of water, add a few drops of diluted hydrochloric acid and pass in hydrogen sulphide: an orange colored precipitate is produced.

Weigh accurately from 0.2 to 0.3 Gm. of antimony sodium thioglycollate, dissolve it in about 100 cc. of warm water, add 1 cc. of diluted hydrochloric acid, pass in hydrogen sulphide until precipitation is complete and allow to stand 30 minutes. Collect the antimony sulphide in a weighed Gooch crucible, wash it successively with water containing hydrogen sulphide, alcohol, ether, carbon disulphide, alcohol and ether, dry the residue at 110 C. and weigh. The antimony sulphide corresponds to not less than 37 per cent of antimony.

ARBUTIN.—Arbutinum.—$C_{12}H_{16}O_7.+\frac{1}{2}H_2O$.—A glucoside occurring in the leaves of *Arctostaphylos uva-ursi, Vaccinium vitis-idaea* and many other genera of the family *Ericaceae.*

Actions and Uses.—Arbutin probably owes its effect, at least in part, to the antiseptic action of hydroquinone, formed by its decomposition in the urinary tract. It has been used as a urinary antiseptic and diuretic.

Dosage.—From 0.2 to 0.5 Gm. (3 to 8 grains) three or four times a day.

Arbutin occurs in long, glistening, colorless needles, or as a fine, white, crystalline, odorless powder having a bitter taste. It is soluble in 8 parts of water and 16 parts of alcohol; very soluble in hot water and hot alcohol; insoluble in chloroform, ether and carbon disulphide. Its aqueous solution is neutral to litmus paper and is not precipitated by solutions of the metallic salts or by solution of tannin. Its aqueous solution is colored blue by ferric chloride test solution. By boiling with diluted sulphuric acid or by treatment with emulsion, arbutin is converted into glucose and hydroquinone.

When heated to 100 C. arbutin loses its water of hydration. At 195 C. the anhydrous glucoside melts. It should leave no residue on ignition. An aqueous solution of arbutin (1 in 20 should not be affected by hydrogen sulphide (*lead*).

Arbutin-Abbott.—A brand of arbutin-N. N. R.

Manufactured by The Abbott Laboratories, North Chicago. No U. S. patent or trademark.

Arbutin-Merck.—A brand of arbutin-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

ARSENIC COMPOUNDS

In some of the compounds listed below, the arsenic is pentavalent; in others it is trivalent. A typical arsenic reaction results only from the trivalent arsenic, and in order to secure this action from those compounds containing pentavalent arsenic, their arsenic must be reduced to the trivalent form; this is done by the body, but the rate at which the reduction occurs varies greatly with the different compounds. In some cases, the desirable, as well as the undesirable, effects produced by these compounds are due to the arsenic which is slowly rendered active; in others the therapeutic effects may be due, at least in part, to the unaltered molecules. The diseases in which arsenic therapy has proved useful are particularly those caused by protozoa. Inorganic arsenic will kill protozoa, but it cannot be administered so as to reach the protozoa in fatal quantity. In the body, the organic compounds are less toxic to mammals and more toxic to protozoan parasites. In this way they become available for combating trypanosomes, syphilis, spirillosis and other protozoan infections.

Among the advantages claimed for, or known to be possessed by, these compounds, the following may be mentioned: In those known to produce their effects through the liberation of arsenic, the arsenic is liberated slowly; some remain in the circulating blood for a much longer period than do inorganic arsenic compounds and thus remain longer in contact with parasites which it is desired to kill; some are specifically etiotropic, that is, they have a much greater affinity for the parasites causing the disease than they have for the tissues of the host.

Arsphenamine and analogous preparations of arsenic used intravenously come under the national law covering serums, viruses, toxins and analogous products, and are subject to the same control.

COMPOUNDS CONTAINING TRIVALENT ARSENIC

According to Ehrlich's view, only trivalent arsenic is markedly toxic to spirochetes, trypanosomes, etc.; hence he introduced a number of such compounds. Of these only the arsphenamines, in which the toxicity is reduced or modified by the introduction into the molecules of certain groups, are listed below. These compounds have, according to Ehrlich, a special affinity to certain organisms, particularly spirochetes, while their toxicity for the higher animals is comparatively low. The exact fields of usefulness of these compounds and their limitations, and also the best methods of administering them, are still under discussion.

The toxic actions of arsphenamine are ascribed to the arsenic component in some cases. In other cases the decomposition of the solution has been assigned as a cause. Undoubtedly some reactions are due to idiosyncrasies on the part of the patient. However, there is seen a large group of these cases which must be explained otherwise. Certainly, improper technique in the preparation of the drug, as well as the improper administration may add to the inherent toxicity. The administrator should always observe the directions supplied by the manufacturers to the letter. If this be done and there are still reactions, then only can we look elsewhere for the causation.

The water used should be, if possible, freshly distilled into Jena glass or Pyrex glass and freshly sterilized. All chemicals should be pure. Any rubber tubing employed for the first time should be soaked over night in five per cent sodium hydroxide solution, then boiled in distilled water and thoroughly washed with the same. Some reactions are undoubtedly due to administration of the drug to a patient on a full stomach or to one not properly prepared by previous catharsis. It is always well to start the use of arsphenamine with a small dose—because of possible idiosyncrasies.

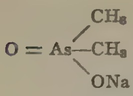
One should not be too much alarmed in a fresh case of syphilis by the reaction seen after the first injection of the arsphenamines—the Herxheimer reaction. It is that phenomenon of the reaction of the disease to the arsphenamine in which there is a rise of temperature, headache, possible nausea, malaise, and marked accentuation of the cutaneous and mucous membrane symptoms. One should be concerned, however, if with succeeding injections there are promptly recurring reactions in the way of gastritis, itching of the skin, urticaria, fixed areas of dermatitis that flare up with each new injection, more or less generalized dermatitis, or jaundice. In fact, there is sometimes noted generalized exfoliative dermatitis, purpura hemorrhagica, acute yellow atrophy and encephalitis.

The best treatment of these conditions is prophylaxis, and these drugs should never be readministered without inquiry of the patient and examination of the skin as to possible pruritis, jaundice, or cutaneous eruptions, or other symptoms. Moreover, a urine examination should always be a preliminary. Sodium thiosulphate has been employed to combat these manifestations. While its greatest usefulness appears to be in the case of jaundice and exfoliative dermatitis, it may have a definite value in clearing up the early reaction, also. Evidence of its value in combating purpura hemorrhagica and encephalitis is not so clear, but it is sufficient to indicate its trial.

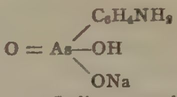
The ratio between etiotropic efficiency and toxicity is far more favorable in the arsphenamines than in any of the other organic arsenic compounds thus far tested. Arsenic has been found in the parts infected with syphilis while absent from other localities, indicating that the efficient arsenical compounds combine with the spirochetes or their products in the tissues.

Arsphenamines are contraindicated or should be used with special caution in diseases of the eye of a nonsyphilitic character; in severe affections of the heart and blood vessels, the lungs, and kidneys; and in advanced degenerative processes in the central nervous system. They should also be used with caution in infants.

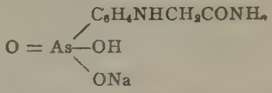
COMPOUNDS CONTAINING PENTAVALENT ARSENIC



Sodium cacodylate



Sodium arsanilate



Tryparsamide

In one of the compounds listed below, the arsenic is in combination with an alkyl group and is thus analogous to the cacodylates; in the others the arsenic is in combination with aniline, and is thus analogous to arsanilic acid.

Arsanilic acid is derived from arsenic acid, AsO.(OH)$_3$ by replacing one hydroxyl by aniline (phenylamine) $C_6H_5NH_2$; related compounds are made by substituting derivatives of aniline.

The compounds containing pentavalent arsenic are comparatively nontoxic when introduced into the animal system until changes take place that liberate the arsenic. When they are slowly decomposed, they produce favorable effects. If the reduction takes place with greater rapidity, they may produce ordinary arsenic poisoning.

Sodium cacodylate is excreted partly unchanged and partly as cacodylic oxide, which gives a foul odor to the breath, perspiration, etc. Further changes yield products containing inorganic, trivalent arsenic, by which the therapeutic effects are produced.

Sodium arsanilate has been used chiefly against trypanosomes. This salt has no direct action on these parasites, but owes its effects to the products resulting from its reduction in the system. These products appear to be organic compounds containing the arsenic in the trivalent form. Artificial reduction products, which vary according to conditions are much more active than the arsanilate.

Sodium arsanilate has also been recommended for the conditions which are influenced favorably by other forms of arsenic, but this salt seems to have no advantages over the official preparations of arsenic.

In poisonous doses or when excessive reduction occurs, sodium arsanilate may produce the ordinary toxic effects of arsenic. It acts with especial violence on the optic nerve, producing optic atrophy, frequently resulting in permanent blindness. This may occur unfortunately even with therapeutic doses.

Compounds Containing Trivalent Arsenic

ARSPHENAMINE.—For description see the U. S. Pharmacopeia and Useful Drugs under Arsphenamina.

Actions and Uses.—Arsphenamine is useful as a specific remedy for syphilis in all stages. According to available data, in incipient tabes, early paralysis, and epilepsy and cerebrospinal syphilis, the drug can be employed with the prospect of benefit only in those cases in which its use is begun immediately after the first symptoms of the secondary disease have appeared.

The drug is used in the spirillum affections, such as relapsing fever and frambesia, and also in malaria; it is also said to be an available substitute for arsenic in the treatment of diseases of the skin and nerves and in the anemias.

The remedy is contraindicated in severe disturbances of the circulatory organs, advanced degenerations of the central nervous system and cachexias, unless these are a direct result of syphilis; it is also contraindicated in patients who have pronounced idiosyncrasy against arsenic.

It has been employed successfully in various types of syphilitic disease of the eyes. Repeated injections should be given. It may be used up to 0.01 Gm. per kilo bodyweight; but it is better to keep under this dose.

Dosage.—From 0.2 to 0.4 Gm. (3 to 6 grains), though 0.6 Gm. (9 grains) may be given, but the smaller doses are being more extensively used.

For children from 0.2 to 0.3 Gm. (3 to 5 grains). In infants doses of from 0.02 to 0.1 Gm. (⅓ to 1½ grains) may be used. The dose should be varied according to the strength and condition of the patient. The intravenous method is, on the whole, preferable and is especially to be recommended.

For intravenous injection one should proceed thus:

The ampule containing the drug is immersed in alcohol, then carefully wiped off, the neck filed across and broken off, and the contents sprinkled on sterile distilled water (10 cc. for each 0.1 gram of the drug used), contained in a sterile Erlenmeyer flask. The drug is allowed to dissolve with little or no agitation. Normal sodium hydroxide is then added to the solution, using 0.85 cc. to every 0.1 Gm. of the drug. Thus 0.6 Gm. of the drug would require 5.1 cc. of normal alkali. A precipitate of the base is first formed, which, after the contents are carefully agitated, is again brought into solution, the fluid being strongly alkaline. Filter the alkalinized solution through sterile gauze, 4 ply, and dilute the filtrate with sterile distilled water to make 25 cc. for each 0.1 Gm. of the drug. It should stand 30 minutes before using. At least one minute should be allowed for each 25 cc. of the solution to flow into the vein, using the gravity method. The directions accompanying the drug as to temperature of the water, etc., should be followed. A few syphilographers use intramuscular injections, but these are not recommended for general use. In all cases the skin should be disinfected with tincture of iodine or with alcohol.

In the treatment of syphilis of the central nervous system, the Swift-Ellis method of intraspinal treatment is utilized at times, the technic of which is described herewith.

An injection of the usual dose of arsphenamine or neoarsphenamine is given intravenously. One hour after the injection, 40 cc. of blood is withdrawn by venipuncture. This is allowed to clot and left on ice for twenty-four hours. The serum is then pipetted off and centrifuged; 12 cc. of this serum is usually added to 18 cc. of sterile normal salt solution to make a 40 per cent solution of arsphenaminized serum, although it may be used without dilution. This is then heated for thirty minutes at 56 C. Before making the intraspinal injection, a volume of spinal fluid equal to that of the injection is often withdrawn. The injection of arsphenamine in small doses (0.0001 Gm. up to a maximum of 0.0005 Gm. mixed with the spinal fluid drawn off and reinjected) directly into the spinal canal is being rather extensively practiced and is said to give results practically as satisfactory as those obtained by the Swift-Ellis method and to be much more simple.

In tabes dorsalis, the results of this method have sometimes been found highly satisfactory—more so than with the ordinary intravenous therapy: the pains have disappeared, the reaction in the cerebrospinal fluid has returned more or less completely to normal, and certain symptoms, such as diminution of bladder control and sexual power, which are usually looked on as fundamental phenomena, may disappear entirely or be greatly improved; patients also feel better.

In cerebrospinal syphilis, also, the intraspinal method has been used to a considerable extent. It is questionable, however, whether the results are much better than those of the intravenous method.

In dementia paralytica, the results of this method have been disappointing.

The contents of a tube should be used at once after opening, and under no circumstances should the contents of a tube damaged in transportation or any remnants of the powder from previously opened tubes be used.

Arsenobenzol-Billon.—A brand of arsphenamine-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J., by license of Les Etablissements Poulenc Frères, Paris.

Arsenobenzol-Billon, 0.1 Gm. Ampules.
Arsenobenzol-Billon, 0.2 Gm. Ampules.
Arsenobenzol-Billon, 0.3 Gm. Ampules.
Arsenobenzol-Billon, 0.4 Gm. Ampules.
Arsenobenzol-Billon, 0.5 Gm. Ampules.
Arsenobenzol-Billon, 0.6 Gm. Ampules.

Diarsenol.—A brand of arsphenamine-U. S. P.

Manufactured by the Diarsenol Laboratories, Inc., Buffalo, N. Y (Diarsenol Company, Inc., Buffalo, N. Y., distributor).

Diarsenol, 0.1 Gm. Ampoules.
Diarsenol, 0.2 Gm. Ampoules.
Diarsenol, 0.3 Gm. Ampoules.
Diarsenol, 0.4 Gm. Ampoules.
Diarsenol, 0.5 Gm. Ampoules.
Diarsenol, 0.6 Gm. Ampoules.
Diarsenol, 1.0 Gm. Ampoules.
Diarsenol, 2.0 Gm. Ampoules.
Diarsenol, 3.0 Gm. Ampoules.

Salvarsan.—A brand of arsphenamine-U. S. P.

Manufactured by H. A. Metz Laboratories, Inc., New York. U. S. trademark 40,734.

Salvarsan, 0.1 Gm. Tubes.
Salvarsan, 0.2 Gm. Tubes.
Salvarsan, 0.3 Gm. Tubes.
Salvarsan, 0.4 Gm. Tubes.
Salvarsan, 0.5 Gm. Tubes.
Salvarsan, 0.6 Gm. Tubes.
Salvarsan, 1 Gm. Tubes.
Salvarsan, 2 Gm. Tubes.
Salvarsan, 3 Gm. Tubes.

BISMARSEN. — Sulpharsphenamine Bismuth. — Bismuth Arsphenamine Sulphonate.—The sodium salt of a bismuth derivative of arsphenamine methylene sulphonic acid (the exact structural formula of which has not been established) with inorganic salts. It contains approximately 13 per cent of arsenic and 24 per cent of bismuth.

Actions and Uses.—For the treatment of syphilis. According to Stokes and Chambers (*J. A. M. A.* **89**:1500 [Oct. 29] 1927) the drug is somewhat slower in its action than intramuscularly administered sulpharsphenamine or intravenously administered neoarsphenamine, but much more rapid than bismuth. More or less severe pains at the site of injection have been reported.

Dosage.—Bismarsen is administered intramuscularly. The initial dose is 0.1 Gm.; for succeeding doses Stokes and Chambers used 0.2 Gm. each of the drug dissolved in ampule with 1 cc. of sterile distilled water at the time of administration, adding to the solution 2 to 3 drops of a 2 per cent solution of butyn. At the time of reporting, however, the authors questioned the desirability of using the local anesthetic. Weekly increasing to biweekly doses were used in treatment courses of twenty doses.

Manufactured by the Abbott Laboratories, North Chicago, Ill. U. S. patent 1,605,691 (Nov. 2, 1926; expires 1943). U. S. trademark applied for.

Bismarsen is prepared by adding a solution of potassium bismuth tartrate in water to an aqueous solution of 3,3' diamino 4,4' dihydroxarsenobenzene N,N' dimethylene sulphonate, dissolving precipitate with a measured quantity of sodium hydroxide solution, precipitating by pouring the clear solution into a methyl alcohol ether mixture, filtering off the precipitate and drying it in vacuo.

Bismarsen is a brownish yellow amorphous powder readily soluble in water, yielding a yellow solution which is slightly alkaline to litmus.

Add 2 cc. of diluted hydrochloric acid to 5 cc. of a 1 per cent solution of bismarsen: a white opalescence appears and dissolves almost immediately; a heavy white gelatinous precipitate develops in two minutes. Add 1 cc. of diluted nitric acid to 5 cc. of a 1 per cent solution of bismarsen: the solution gradually turns brown and yields a precipitate. Add 1 cc. of trinitrophenol solution to 5 cc. of a 1 per cent solution of bismarsen: no apparent reaction takes place (*distinction from silver arsphenamine and potassium bismuth tartrate*). Bubble hydrogen sulphide through a 1 per cent solution of bismarsen: the solution darkens immediately but no precipitate is formed Add 5 cc. of hydrogen peroxide solution to 5 cc. of a 1 per cent solution of bismarsen: the solution is at first turbid, then becomes a deep reddish brown with formation of a precipitate. Add 1 cc. of mercuric potassium iodide solution to 5 cc. of a 1 per cent solution of bismarsen: the solution yields a greenish yellow opalescence, which in turn assumes a dirty green color on standing. Add drop by drop 2 cc. of a 40 per cent sodium hydroxide solution to 5 cc. of a 1 per cent solution of bismarsen: the solution gradually darkens without any formation of precipitate. Add 0.5 cc. of a 2 per cent silver nitrate solution to 5 cc. of a 1 per cent solution of bismarsen: a dark red solution is produced (*distinction from arsphenamine*). Add 1 cc. of a saturated solution of bromine in water to 5 cc. of a 1 per cent solution of bismarsen: the solution yields a greenish brown precipitate (*distinction from sulpharsphenamine, neoarsphenamine and arsphenamine*). Add 0.5 Gm. of zinc dust and 5 cc. of diluted hydrochloric acid to 0.1 Gm. of bismarsen in a test tube, at the mouth of the tube hold a strip of filter paper moistened with 5 per cent cadmium chloride solution: the paper turns yellow in four minutes.

Transfer about 0.4 Gm. of bismarsen, accurately weighed, to a Kjeldahl flask, add 2 cc. of sulphuric acid and heat carefully; add 2 cc. of nitric acid a drop at a time, continue heating until brown fumes cease to be given off, cool and add water to make 120 cc.; if a white crytalline precipitate appears dissolve it with a few drops of hydrochloric acid; transfer to a 250 cc. beaker, add 7 Gm. of tartaric acid, neutralize with strong ammonia water, add 10 cc. of magnesia mixture followed by 20 cc. stronger ammonia water, allow to stand twelve hours, filter through a hard surface filter paper and wash the precipitate with 50 cc. of 2.5 per cent ammonia water, puncture the filter, transfer the precipitate into a 250 cc. beaker with washings, then add just sufficient hydrochloric acid to dissolve the precipitate, filter, wash the filter well with water, neutralize the filtrate with stronger ammonia water; add 1 cc. of magnesia mixture and 20 cc. of stronger ammonia water; allow to stand twelve hours; filter, using a prepared Gooch crucible; wash with 2.5 per cent ammonia water; dry at 100 C.; ignite at 700 C. for three hours; cool in a desiccator and weigh as magnesium pyroarsenate and calculate to arsenic: the arsenic content is not less than 12.50 per cent, nor more than 13.50 per cent. Transfer about 0.25 Gm. of bismarsen accurately weighed to an Erlenmeyer flask. Add 5 cc. of diluted sulphuric acid followed by 1 Gm. of powdered potassium permanganate, and 10 cc. of sulphuric acid in small portions; add just sufficient hydrogen peroxide to dissolve the brown precipitate; add 50 cc. of water; boil for twenty minutes; cool to 70 C.; saturate with hydrogen sulphide for twelve hours; filter, using a prepared Gooch crucible; wash the precipitate with water, warm ammonium polysulphide, methyl alcohol, carbon bisulphide and acetone in the order named; dry at 100 C.; cool in a desiccator and weigh as bismuth sulphide (Bi_2S_3); calculate to bismuth: the percentage of bismuth found corresponds with the percentage of arsenic found multiplied by 1.86 (factor As to Bi in $C_{21}H_{21}O_{12}As_3Na_3S_3N_3Bi_2$) plus or minus 0.5 per cent.

NEOARSPHENAMINE.—For description see the U. S. Pharmacopeia and Useful Drugs under Neoarsphenamina.

Actions and Uses.—Neoarsphenamine is a modified soluble compound of arsphenamine, its actions and uses are those of arsphenamine.

Dosage.—Neoarsphenamine is given in larger doses than arsphenamine because it contains less arsenic and is less toxic. The average dose for a man is 0.6 to 0.75 Gm. (9 to 12 grains), with 0.45 Gm. (7 grains) as the minimum and possibly 0.9 Gm. (14 grains) for very large men. For women, 0.6 Gm. (9 grains) is the average if the patient is above the normal in weight; 0.3 Gm. (3 grains) would be the minimum, and 0.75 Gm. (12 grains) as the maximum only in those females who are of large size. Children may be given 0.1 to 0.2 Gm. (1.5 to 3 grains). The limit dose is 0.15 Gm. (2.5 grains) per kilo bodyweight. Here again the smaller dose is now used.

Neoarsphenamine may be administered by intravenous or intramuscular injection, the former being considered decidedly preferable; the drug must not be administered subcutaneously. For intravenous injection, 12.5 cc. of freshly distilled water should be used for each 0.1 Gm. of neoarsphenamine. For the intramuscular injections, 3 cc. of freshly distilled water should be used for each 0.15 Gm. of neoarsphenamine, this yielding an approximately isotonic solution.

Neoarsphenamine may be employed intravenously in concentrated solutions. For this purpose as much as 0.1 Gm. may be dissolved in 0.5 cc. of sterile freshly distilled water; the injection is made with a syringe instead of by gravity. It is well to draw out an equal amount of blood into the syringe containing the neoarsphenamine solution before reinjecting into the bloodstream.

The ampule containing the drug is immersed in alcohol; then carefully wiped off; the neck filed across and broken off; and the contents sprinkled on the surface of cool, sterile distilled water and allowed to dissolve *without shaking* the solution. Any product incompletely soluble should be discarded. Solutions of neoarsphenamine must be injected *immediately* after their preparation. Neoarsphenamine must not be warmed and the temperature of the injected fluid should not be more than 20 to 22 C. (68 to 71.6 F.).

The drug may undergo deterioration in the ampule, and care should be exercised to use the drug of normal color and free solubility. This drug should preferably be kept in a cool dark room and be not more than 6 months old.

When tested by the method used for arsphenamine but omitting the use of sodium hydroxide in preparing this solution, 60 per cent of the albino rats should survive 0.240 Gm. per kilogram body weight for six days when the drug is administered intravenously as a 4 per cent solution.

All neoarsphenamine in use in the United States is manufactured under U. S. patent reissue 13,848 (Dec. 15, 1914; expires 1931) by license of the U. S. Federal Trade Commission or the Chemical Foundation. Also licensed for interstate sale by the U. S. Treasury Department under the "act to regulate the sale of viruses, serums, toxins and analogous products" as conforming to the regulations for the control, sale and manufacture of neoarsphenamine; issued Aug. 1, 1923.

Neodiarsenol.—A brand of neoarsphenamine-U. S. P.

Manufactured by the Diarsenol Laboratories, Inc., Buffalo, N. Y. (Diarsenol Company, Inc., Buffalo, N. Y., distributor).

Neodiarsenol, 0.15 Gm. Ampoules.
Neodiarsenol, 0.3 Gm. Ampoules.
Neodiarsenol, 0.45 Gm. Ampoules.
Neodiarsenol, 0.6 Gm. Ampoules.
Neodiarsenol, 0.75 Gm. Ampoules.
Neodiarsenol, 0.9 Gm. Ampoules.

Neosalvarsan.—A brand of neoarsphenamine-U. S. P.

Manufactured by H. A. Metz Laboratories, Inc., New York. U. S trademark 88,862.

Neosalvarsan, Dose I.—Each contains neosalvarsan, 0.15 Gm.
Neosalvarsan, Dose II.—Each contains neosalvarsan, 0.3 Gm.
Neosalvarsan, Dose III.—Each contains neosalvarsan, 0.45 Gm.
Neosalvarsan, Dose IV.—Each contains neosalvarsan, 0.6 Gm.
Neosalvarsan, Dose V.—Each contains neosalvarsan, 0.75 Gm.
Neosalvarsan, Dose VI.—Each contains neosalvarsan, 0.9 Gm.
Neosalvarsan, Dose X.—Each contains neosalvarsan, 1.5 Gm.
Neosalvarsan Dose XII.—Each sealed tube contains neosalvarsan, 1.8 Gm.
Neosalvarsan, Dose XX.—Each contains neosalvarsan, 3.0 Gm.
Neosalvarsan, Dose XXX.—Each contains neosalvarsan, 4.5 Gm.

Novarsenobenzol-Billon.—A brand of neoarsphenamine-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J., by license of Les Etablissements Poulenc Freres, Paris.

Novarsenobenzol-Billon 0.15 Gm. Ampules.
Novarsenobenzol-Billon 0.3 Gm. Ampules.
Novarsenobenzol-Billon 0.45 Gm. Ampules.
Novarsenobenzol-Billon, 0.6 Gm. Ampules.
Novarsenobenzol-Billon 0.75 Gm. Ampules.
Novarsenobenzol-Billon, 0.9 Gm. Ampules.

SILVER ARSPHENAMINE.—Argentum Arsphenamina.—Sodium Silver Arsphenamine.—The sodium salt of silver-diamino-dihydroxy-arseno-benzene (the exact molecular formula has not been established). Silver arsphenamine contains not less than 19 per cent of arsenic and from 12 to 14 per cent of silver.

Actions and Uses.—Silver arsphenamine has practically the same uses as those of arsphenamine. Its claimed advantage over other arsphenamine preparations is said to be due to the introduction of the silver (nonionizable form) as a component, thereby improving the chemo-therapeutic index, presumably because of the fact that silver and its compounds have a decided antisyphilitic influence.

In the presence of organic diseases of the heart, aneurysm, aortitis, as well as in other parenchymatous diseased conditions of the glandular structures (liver and kidney), silver arsphenamine should be used only with great caution and in small doses, the patient and all functions being observed most carefully.

If angioneurotic symptoms appear shortly after the injection, they should disappear rapidly; usually they may be avoided by the use of considerably diluted solutions. Susceptible individuals should not be treated during working hours. Hypersensitive patients should recline for some time after the injection. Argyria may occur rarely as a sequel to the use of the preparation.

Dosage.—From 0.1 Gm. to 0.3 Gm. for adults. The treatment should begin with an injection of 0.1 Gm., gradually increasing the dosage, at intervals of not less than four days, to 0.2 Gm. maximum in women and 0.3 Gm. in men. The larger doses are indicated only if the preparation is well tolerated by the patient. The dosages 0.2 to 0.25 Gm. may be given at regular intervals of four days and repeated until the desired therapeutic results have been achieved. Patients with disorders of the nervous system or those suffering from severe headaches should be given smaller initial doses, 0.05 and 0.075 Gm. When these amounts are well tolerated, larger doses may be employed, increasing very gradually.

In preparing the solution for injection, the ampule is first sterilized by immersion in alcohol for 15 minutes; after opening the ampule, the contents are sprinkled on the surface of 5 cc. of cool (20-22 C.), sterile, distilled water, contained in a small sterile flask. The silver arsphenamine will go into solution rapidly; heating and shaking must be avoided. A quantity of cool sterile solution of sodium chloride, 0.4 per cent, is then added so that the final solution will approximate 20 cc. of liquid per decigram (0.1 Gm.) of the drug. *The solution must be administered promptly.*

Silver arsphenamine is prepared by treating the dihydrochloride of 3-diamino-4-dihydroxy-1-arsenobenzene (arsphenamine) with silver salts, converting the resulting compound to the disodium salt, and precipitating by means of alcohol, ether or acetone. The silver is not in an ionizable form.

Silver arsphenamine is a brownish-black powder, unstable in air; when properly dried it is free from lumps. It is readily soluble in water, yielding a dark brown solution (*distinction from arsphenamine, sodium arsphenamine and neoarsphenamine*); the solution has an alkaline reaction (*distinction from arsphenamine*).

The addition of dilute sodium hydroxide solution to 3 cc. of an aqueous solution of silver arsphenamine (1 in 500) produces no precipitate (*distinction from arsphenamine*). On the addition of 1 cc. of sodium carbonate test solution to 1 cc. of silver arsphenamine solution (1 in 20) no precipitate is formed (*distinction from arsphen-*

amine). The addition of 1 cc. of saturated solution of sodium bicarbonate to 1 cc. of silver arsphenamine produces a precipitate.

One cc. of an aqueous solution of silver arsphenamine solution (1 in 20) when slightly acidulated with dilute hydrochloric acid yields a precipitate (*distinction from arsphenamine*). This precipitate dissolves on the very careful addition of more acid; on heating no irritating odor of sulphur dioxide should be detected (*distinction from neoarsphenamine*). However, a large excess of hydrochloric acid yields a precipitate. The careful addition of 3 cc. of acetic acid test solution to 3 cc. of silver arsphenamine solution (1 in 20) produces a precipitate (*distinction from arsphenamine*), a portion of which dissolves on further addition of the acetic acid test solution. When 3 cc. of silver arsphenamine solution (1 in 20) is heated with a few crystals of potassium permanganate (*without addition of alkali; distinction from arsphenamine*), the permanganate is reduced and ammonia is evolved which may be tested by placing a moistened piece of red litmus paper in the vapors: the litmus paper will turn blue. The precipitate thus formed may be treated with hot nitric acid test solution; the mixture boiled for a few minutes, then cooled, diluted and filtered: the filtrate will yield a precipitate of silver chloride on the addition of hydrochloric acid (*distinction from arsphenamine, neoarsphenamine, and sodium arsphenamine*). The addition of 1 cc. of trinitrophenol (picric acid) test solution to 1 cc. of silver arsphenamine solution produces a yellow precipitate (*distinction from neoarsphenamine*). The addition of 1 drop of ferric chloride test solution to 1 cc. of silver arsphenamine solution (1 in 500) produces a deepening of the brown color, with a slightly purplish tint (*distinction from sodium arsphenamine*), the liquid finally becoming turbid; if a more concentrated solution of silver arsphenamine (1 in 20) is employed, an immediate precipitate is formed. The careful addition, drop by drop, of bromine water to 3 cc. of silver arsphenamine (1 in 250) produces a reddish coloration, which is discharged by an excess of the reagent; there is also formed a precipitate which dissolves on addition of a large excess of concentrated ammonia water (*distinction from arsphenamine, neoarsphenamine and sodium arsphenamine*). To 1 cc. of silver arsphenamine solution (1 in 20) add 1 cc. of hydrogen peroxide test solution: a brown precipitate resembling silver oxide is formed and the supernatant liquid is almost colorless (*distinction from arsphenamine, neoarsphenamine and sodium arsphenamine*). To 1 cc. of silver arsphenamine solution (1 in 20) add 1 cc. of sodium chloride, test solution: no precipitate forms (*absence of ionizable silver*). (A concentrated sodium chloride solution added to a strong solution of silver arsphenamine causes a precipitate to form, due to "salting out" action.)

Place about 0.2 Gm. of silver arsphenamine, accurately weighed, in an Erlenmeyer flask, and carry out the Lehman process (described in the Public Health Reports **33**: 1003 [June 21] 1918) through the point of digestion. While the solution is hot, add cautiously dilute hydrochloric acid solution in order to obtain the precipitation of silver chloride. Filter off the silver chloride through a tared asbestos Gooch crucible, wash well and weigh: from the weight of silver chloride, the percentage of silver may be calculated. The filtrate from the silver chloride is carried on in the usual manner according to the Lehman method, thereby determining the arsenic content. The total silver content of the drug shall be 12 to 14 per cent and the total arsenic content shall be not less than 19 per cent.

To determine the toxicity, select not less than five healthy albino rats weighing between 100-150 grams (pregnant animals shall not be used), prepare a 2 per cent silver arsphenamine solution and inject the solution into the saphenous vein of each rat at the rate of not more than 0.5 cc. per minute. The rats shall not be anesthetized for the injection. At least 60 per cent of the series of animals injected with the maximum tolerated dose should survive forty-eight hours from the time of injection; the maximum tolerated dose shall not be below 0.14 Gm. per kilo body weight.

Silver-Salvarsan.—A brand of silver arsphenamine-N. N. R.

Manufactured by the H. A. Metz Laboratories, New York. U. S. patent 1,127,603 (Feb. 9, 1915; expires 1932). U. S. trademark 161,232.

Licensed for interstate sale by the U. S. Treasury Department under the "act to regulate the sale of viruses, serums, toxins and analogous products" as conforming to the regulations for the control, sale and manufacture of silver arsphenamine.

Silver-Salvarsan 0.05 Gm. Ampules.
Silver-Salvarsan 0.1 Gm. Ampules.
Silver-Salvarsan 0.15 Gm. Ampules.
Silver-Salvarsan 0.2 Gm. Ampules.
Silver-Salvarsan 0.25 Gm. Ampules.
Silver-Salvarsan 0.3 Gm. Ampules.
Silver-Salvarsan 0.6 Gm. Ampules.

SODIUM ARSPHENAMINE. — Sodiarsphenamina.—Sodium Arsenphenolamine. The sodium salt of 3-diamino-4-dihydroxy - 1 - arsenobenzene, $NaO.NH_2C_6H_3As : As.C_2H_3NH_2ONa$, with a stabilizing medium. Sodium arsphenamine contains not less than 19 per cent of arsenic (As).

Actions and Uses.—The same as those of arsphenamine; its advantage over arsphenamine is that it does not require addition of alkali before use.

Dosage. — From 0.45 to 0.9 Gm. for adults. As 3 parts sodium arsphenamine are equivalent to 2 parts arsphenamine, the amount of drug to be administered should be 50 per cent more than arsphenamine under the same conditions. In preparing the solution for injection, the sodium arsphenamine must be dissolved immediately after opening the ampule and everything except gentle shaking should be avoided in effecting solution. The quantity of sterile distilled water used for solution should be in the proportion of 20 cc. for each 0.1 Gm. of the drug. Heating must be avoided in the preparation of the solution; any difficultly soluble preparation should not be employed. *The solution must be administered promptly.*

Sodium arsphenamine is a bright yellow powder, very unstable in air; when properly dried, it is free from lumps. It is readily soluble in water, yielding an orange-yellow solution; the solution has an alkaline reaction (*distinction from arsphenamine*).

The addition of dilute sodium hydroxide solution to 3 cc. of an aqueous solution of sodium arsphenamine (1 in 500) produces no precipitate (*distinction from arsphenamine*). On the addition of 1 cc. of sodium carbonate solution to 1 cc. of sodium arsphenamine solution (1 in 20) no precipitate is formed (*distinction from arsphenamine*). The addition of 1 cc. of saturated sodium bicarbonate solution to 1 cc. of sodium arsphenamine solution produces a precipitate.

One cc. of an aqueous solution of sodium arsphenamine solution (1 in 20) when made acid (to phenolphthalein) with dilute hydrochloric acid yields a precipitate (*distinction from arsphenamine*). This precipitate dissolves on the very careful addition of more acid; on heating, no irritating odor of sulphur dioxid should be detected (*distinction from neoarsphenamine*). [However, an excess of hydrochloric acid, or the concentrated acid yields a precipitate.] The careful addition of 3 cc. of acetic acid solution to 3 cc. of sodium arsphenamine solution (1 in 20) produces a precipitate (*distinction from arsphenamine*). When 3 cc. of sodium arsphenamine solution (1 in 20) is heated with a few crystals of potassium permanganate without addition of alkali (*distinction from arsphenamine*), the permanganate is reduced and ammonia is evolved which may be tested for by placing a moistened piece of red litmus paper in the vapors: the litmus paper will turn blue. The addition of 1 cc. of trinitrophenol (picric acid) solution to 1 cc. of sodium arsphenamine solution (1 in 500) produces a yellow precipitate (*distinction from neoarsphenamine*). The addition of 1 drop of ferric chlorid solution to 1 cc. of sodium arsphenamine solution (1 in 500) produces a brownish-violet color, which changes gradually to red, the liquid finally becoming turbid; if a more concentrated solution of sodium arsphenamine (i. e., 1 in 20) is employed, an immediate precipitate is formed. The careful addition, drop by drop, of bromine water to 1 cc. of sodium arsphenamine solution produces a red solution, the color of which is discharged by an excess of the reagent. To 1 cc. of sodium arsphenamine solution (1 in 500) is added 1 cc. of dilute nitric acid and 1 cc. of silver nitrate solution; a dark yellow precipitate is formed which becomes black; the black precipitate is dissolved by warming with an equal volume of concentrated nitric acid, generally leaving a white precipitate (any precipitate which may remain is due probably to the use of sodium chloride with which the pure sodium arsphenamine is mixed). The addition of 1 cc. of concentrated nitric acid, drop by drop, to 1 cc. of sodium arsphenamine (1 in 500) forms a momentary precipitate which quickly dissolves, forming a red solution; when a more concentrated solution of sodium arsphenamine (1 in 20) is used, the addition of the nitric acid first causes a yellowish-white precipitate which dissolves in an excess of the acid yielding a dark red solution. The arsenic content of sodium arsphenamine may be estimated according to the Lehman method (*Public Health Reports* **33**: 1003 [June 21] 1918). The total arsenic content of the drug shall not be below 19 per cent.

To determine the toxicity, select not less than five healthy albino rats weighing between 100 and 150 grams (pregnant animals should not be used); prepare a 4 per cent. solution and inject the solution into the saphenous vein of each rat at the rate of not more than 0.5 cc. per minute. The rats should not be anesthetized for the injection At least 60 per cent of the series of animals injected with the maximum tolerated dose should survive forty-eight hours from the time of injection, the maximum tolerated dose should not be below 0.18 Gm per kilogram of body weight.

All sodium arsphenamine in use in the United States is manufactured under patents 1,059,983 and 1,708,135 by license of The Chemical Foundation, Inc. Also licensed for interstate sale by the U. S. Treasury Department under the "act to regulate the sale of viruses, serums, toxins and analogous products" as conforming to the regulations for the control, sale and manufacture of sodium arsphenamine; issued Aug. 1, 1923.

Sodium Diarsenol.—A brand of sodium arsphenamine-N. N. R.

Manufactured by the Diarsenol Laboratories, Inc., Buffalo, N. Y (Diarsenol Co., Inc., Buffalo, N. Y., distributors).

Sodium Diarsenol, 0.15 Gm. Ampules.
Sodium Diarsenol, 0.3 Gm. Ampules.
Sodium Diarsenol, 0.45 Gm. Ampules.
Sodium Diarsenol, 0.6 Gm. Ampules.
Sodium Diarsenol, 0.75 Gm. Ampules.
Sodium Diarsenol, 0.9 Gm. Ampules.

SULPHARSPHENAMINE.—Sulpharsphenamina.—The salt, disodium 3,3′-diamino-4,4′-dihydroxyarsenobenzene-*N*-dimethylenesulphonate, $NaOSO_2CH_2NH.OH.C_6H_3.As:As.C_6H_3OH.NH.CH_2.O_2SONa$, with inert salt. Sulpharsphenamine contains not less than 19 per cent of arsenic (As). According to claims, it differs from neoarsphenamine in having two side chains instead of one, and in that the sulphur has a valence of four (with an extra oxygen atom) and not two as in neoarsphenamine.

Actions and Uses.—The same as those of neoarsphenamine, over which it is claimed to have the advantage of a higher chemotherapeutic index, more prolonged or delayed action, a somewhat greater stability of solution in the presence of air, and of permitting subcutaneous injection. Inasmuch as this drug has caused reactions—especially of the hemorrhagic types—it should be used with great care. It has a place, however, and occasionally can be used by the intramuscular route when the patient will not tolerate arsphenamine or neoarsphenamine.

Dosage.—For intramuscular or subcutaneous use the drug is dissolved in sterile, freshly distilled water in the proportion of about 0.1 Gm. to 0.3 cc.; for intravenous use the same as for intravenous injections of neoarsphenamine.

Sulpharsphenamine is an orange yellow powder possessing an odor resembling that of sulphur dioxide and arsine. It is readily soluble in water yielding a yellow solution which is acid to litmus (*distinction from neoarsphenamine, which is neutral, and sodium arsphenamine, which is alkaline*). On standing over night, the solution darkens and a precipitate is formed.

A *freshly* prepared solution of sulpharsphenamine (1 in 100) yields no immediate precipitate on the addition of diluted acetic acid, whereas neoarsphenamine yields a precipitate sooner (*distinction from arsphenamine*). The general reactions with silver nitrate and ferric chloride, the qualitative tests for the presence of sulphur, are the same as those described under neoarsphenamine.

The arsenic content of sulpharsphenamine may be estimated according to the Lehman method (*Public Health Reports* **33**: 1003 [June 21] 1918). The total arsenic content of the drug shall not be less than 19 per cent.

When tested by the method used for arsphenamine but omitting the use of sodium hydroxide in preparing this solution, 60 per cent of the albino rats should survive 0.3 Gm. per kilogram body weight for three days when the drug is administered intravenously as a 4 per cent solution.

Sulfarsenol.—A brand of sulpharsphenamine-N. N. R.

Manufactured by Laboratoire de Biochemie Medicale, Paris, France (The Anglo-French Drug Co., 1270 Broadway, New York City, distributor). Licensed for interstate sale by U. S. Treasury Department under the "act to regulate the sale of viruses, serums, toxins and analogous products" as conforming to the regulations for the control, sale and manufacture of sulpharsphenamine. No U. S. patent. U. S. trademark 165,521.

Sulfarsenol, .06 Gm. Ampule.
Sulfarsenol, .12 Gm. Ampule.
Sulfarsenol, .18 Gm. Ampule.
Sulfarsenol, .30 Gm. Ampule.
Sulfarsenol, .42 Gm. Ampule.
Sulfarsenol, .60 Gm. Ampule.

Sulpharsphenamine-Abbott.—A brand of sulpharsphenamine-N. N. R.

Manufactured by the Dermatological Research Laboratories, branch of The Abbott Laboratories, North Chicago, under U. S. patent 1,024,993 (April 30, 1912; expires 1929) by license of the Chemical Foundation, Inc.

Sulpharsphenamine-Abbott, 0.2 Gm. Ampules.
Sulpharsphenamine-Abbott, 0.3 Gm. Ampules.
Sulpharsphenamine-Abbott, 0.4 Gm. Ampules.
Sulpharsphenamine-Abbott, 0.6 Gm. Ampules.

Sulpharsphenamine-Billon.—A brand of sulpharsphenamine-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J., under U. S. patent 1,024,993 (April 30, 1912; expires 1929) by license of the Chemical Foundation, Inc.

Sulpharsphenamine-Billon, 0.1 Gm. Ampules.
Sulpharsphenamine-Billon, 0.2 Gm. Ampules.
Sulpharsphenamine-Billon, 0.3 Gm. Ampules.
Sulpharsphenamine-Billon, 0.4 Gm. Ampules.
Sulpharsphenamine-Billon, 0.5 Gm. Ampules.
Sulpharsphenamine-Billon, 0.6 Gm. Ampules.

Sulpharsphenamine-DePree.—A brand of sulpharsphenamine-N. N. R.

Manufactured by DePree Laboratories, Inc., Holland, Mich. (The DePree Company, Holland, Mich., distributor), under U. S. patent 1,024,993 (April 30, 1912; expires 1929) by license of the Chemical Foundation, Inc.

Sulpharsphenamine-DePree, 0.1 Gm. Ampules.
Sulpharsphenamine-DePree, 0.15 Gm. Ampules.
Sulpharsphenamine-DePree, 0.2 Gm. Ampules.
Sulpharsphenamine-DePree, 0.3 Gm. Ampules.
Sulpharsphenamine-DePree, 0.4 Gm. Ampules.
Sulpharsphenamine-DePree, 0.45 Gm. Ampules.
Sulpharsphenamine-De Pree, 0.5 Gm. Ampules.
Sulpharsphenamine-DePree, 0.6 Gm. Ampules.
Sulpharsphenamine-De Pree, 0.9 Gm. Ampules.
Sulpharsphenamine-DePree, 1.0 Gm. Ampules.
Sulpharsphenamine-DePree, 3.0 Gm. Ampules.

Sulpharsphenamine-Mallinckrodt.—A brand of sulpharsphenamine-N. N. R.

Manufactured by the Mallinckrodt Chemical Works, St. Louis, under U. S. patent 1,024,993 (April 30, 1912; expires 1929) by license from The Chemical Foundation, Inc.

Sulpharsphenamine-Mallinckrodt, 0.1 Gm. Ampules.
Sulpharsphenamine-Mallinckrodt, 0.2 Gm. Ampules.
Sulpharsphenamine-Mallinckrodt, 0.3 Gm. Ampules.
Sulpharsphenamine-Mallinckrodt, 0.4 Gm. Ampules.
Sulpharsphenamine-Mallinckrodt, 0.5 Gm. Ampules.
Sulpharsphenamine-Mallinckrodt, 0.6 Gm. Ampules.

Sulpharsphenamine-Metz.—A brand of sulpharsphenamine-N. N. R.

Manufactured by the H. A. Metz Laboratories, New York, under U. S. patent 1,024,993 (April 30, 1912; expires 1929) by license from The Chemical Foundation, Inc.

Sulpharsphenamine-Metz, 0.05 Gm. Ampules.
Sulpharsphenamine-Metz, 0.075 Gm. Ampules.
Sulpharsphenamine-Metz, 0.1 Gm. Ampules.
Sulpharsphenamine-Metz, 0.15 Gm. Ampules.
Sulpharsphenamine-Metz, 0.3 Gm. Ampules.
Sulpharsphenamine-Metz, 0.45 Gm. Ampules.
Sulpharsphenamine-Metz, 0.6 Gm. Ampules.

Sulpharsphenamine-Searle.—A brand of sulpharsphenamine-N. N. R.

Manufactured by G. D. Searle & Co., Chicago, under U. S. patent 1,024,993 (April 30, 1912; expires 1929) by license of the Chemical Foundation, Inc.

Sulpharsphenamine-Searle, 0.1 Gm. Ampules.
Sulpharsphenamine-Searle, 0.2 Gm. Ampules.
Sulpharsphenamine-Searle, 0.3 Gm. Ampules.
Sulpharsphenamine-Searle, 0.4 Gm. Ampules.
Sulpharsphenamine-Searle, 0.5 Gm. Ampules.
Sulpharsphenamine-Searle, 0.6 Gm. Ampules.

Sulpharsphenamine-Squibb.—A brand of sulpharsphenamine-N. N. R.

Manufactured by E. R. Squibb & Sons, New York, under U. S. patent 1,024,993 (April 30, 1912; expires 1929) by license of the Chemical Foundation, Inc.

Sulpharsphenamine-Squibb, 0.1 Gm. Ampules.
Sulpharsphenamine-Squibb, 0.2 Gm. Ampules.
Sulpharsphenamine-Squibb, 0.3 Gm. Ampules.
Sulpharsphenamine-Squibb, 0.4 Gm. Ampules.
Sulpharsphenamine-Squibb, 0.5 Gm. Ampules.
Sulpharsphenamine-Squibb, 0.6 Gm. Ampules.
Sulpharsphenamine-Squibb, 0.9 Gm. Ampules.
Sulpharsphenamine-Squibb, 3 Gm. Ampules.

Compounds Containing Pentavalent Arsenic

ACETARSONE.—Acetylaminohydroxyphenylarsonic Acid. —$HO.CH_3CONH.C_6H_3.As:O:(OH)_2$.—The acetyl derivative of 3-amino-4-hydroxyphenyl-1-arsonic acid.—Acetarsone contains from 27.1 to 27.4 per cent of arsenic (As).

Actions and Uses.—Acetarsone has been reported to produce favorable effects in the treatment of amebic dysentery. It is claimed to yield satisfactory results both in the eradication of dysenteriae cysts and encysted flagellates, and for general amebic dysentery. Acetarsone is not proposed for the treatment of syphilis, and its use in amebic infections is still in the experimental stage.

Dosage.—Orally, 0.25 Gm. for adults; two or three doses a day for a period of seven days has been reported to give satisfactory results.

Acetarsone is a white, odorless powder, having a slightly acid taste. It is slightly soluble in water and alcohol; readily soluble in solutions of alkalis or alkaline carbonates. It is stable at ordinary temperatures.

To a solution of 1 Gm. of acetarsone in 10 cc. of sodium hydroxide solution and 10 cc. of water, add 2 Gm. of sodium hydrosulphite and warm the mixture to about 50 C.: a light yellow precipitate is formed, which is soluble in an excess of sodium hydroxide. To a solution of 0.5 Gm. of acetarsone in 10 cc. of water and a slight excess of ammonia water, add magnesia mixture: no precipitate forms (*absence of inorganic arsenates*); but on heating the mixture for some time, a precipitate is produced. Dissolve 1 Gm. of acetarsone in 10 cc. of sodium carbonate solution: no undissolved residue remains. To 1 Gm. of acetarsone add 10 cc. of hydrochloric acid (5 per cent), shake well and filter. To the filtrate add two drops of solution of potassium bichromate (3 per cent): no red or brown color is produced (*unacetylized amino-acids*). Shake 0.5 Gm. of acetarsone with 10 cc. of diluted nitric acid for five minutes, and then filter: the filtrate becomes at most slightly turbid on the addition of a few drops of silver nitrate solution. Incinerate 0.5 Gm. of acetarsone: not more than 0.2 per cent. of residue remains. Dry a weighed quantity of acetarsone to constant weight at 100 C.: the loss does not exceed 0.5 per cent.

Determine the arsenic of acetarsone by Lehmann's method: the arsenic content corresponds to from 27.1 to 27.4 per cent.

Acetarsone-Abbott.—A brand of acetarsone-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

Tablets Acetarsone-Abbott, 0.25 Gm.

Stovarsol.—A brand of acetarsone-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J., under license of Les Etablissements Poulenc Frères, Paris. No U. S. patent. U. S. trademark 177,082.

Stovarsol Tablets 0.25 Gm.

SODIUM CACODYLATE.—See the U. S. Pharmacopeia and Useful Drugs under Sodii Cacodylas.

Ampules Sodium Cacodylate-Mulford, ¾ grain, 1 cc.: Sodium cacodylate 0.05 Gm. (¾ grain) in 1 cc. of sterile solution, with 1 per cent of benzyl alcohol, added as local anesthetic.

Prepared by H. K. Mulford Company, Philadelphia.

Ampules Sodium Cacodylate-Mulford, 1½ grains.

Prepared by H. K. Mulford Company, Philadelphia.

Ampules Sodium Cacodylate-Mulford, 3 grains, 1 cc.: Sodium cacodylate 0.2 Gm. (3 grains) in 1 cc. of sterile solution, with 1 per cent of benzyl alcohol, added as local anesthetic.

Prepared by H. K. Mulford Company, Philadelphia.

Ampules Sodium Cacodylate-Mulford, 5 grains, 1 cc.: Sodium cacodylate 0.32 Gm. (5 grains) in 1 cc. of sterile solution, with 1 per cent of benzyl alcohol, added as local anesthetic.

Prepared by H. K. Mulford Company, Philadelphia.

Ampules Sodium Cacodylate-Mulford, 7¾ grains.

Prepared by H. K. Mulford Company, Philadelphia.

Ampules Sodium Cacodylate-Mulford, 15 grains.

Prepared by H. K. Mulford Company, Philadelphia.

Ampuls Sodium Cacodylate-Squibb, 0.05 Gm.: Sodium cacodylate 0.05 Gm. (¾ grain) in 1 cc. of sterile solution.

Prepared by E. R. Squibb & Sons, New York.

Ampuls Sodium Cacodylate-Squibb, 0.13 Gm.: Sodium cacodylate 0.13 Gm. (2 grains) in 1 cc. of sterile solution.

Prepared by E. R. Squibb & Sons, New York.

Glaseptic Ampoules Sodium Cacodylate-P. D. & Co., 0.1 Gm. (1½ grains), 1 cc.
Prepared by Parke, Davis & Co., Detroit.

Glaseptic Ampoules Sodium Cacodylate-P. D. & Co. 0.13 Gm. (2 grains), 1 cc.
Prepared by Parke, Davis & Co., Detroit.

Glaseptic Ampoules Sodium Cacodylate-P. D. & Co., 0.2 Gm. (3 grains), 1 cc.
Prepared by Parke, Davis & Co., Detroit.

Glaseptic Ampoules Sodium Cacodylate-P. D. & Co., 0.3 Gm. (5 grains), 1 cc.
Prepared by Parke, Davis & Co., Detroit.

Glaseptic Ampoules Sodium Cacodylate-P. D. & Co., 0.45 Gm. (7 grains), 1 cc.
Prepared by Parke, Davis & Co., Detroit.

Glaseptic Ampoules Sodium Cacodylate-P. D. & Co., 1 Gm. (15½ grains), 2 cc.
Prepared by Parke, Davis & Co., Detroit.

Glaseptic Ampoules Sodium Cacodylate-P. D. & Co. (for Intravenous Use), 0.2 Gm. (3 grains), 5 cc.
Prepared by Parke, Davis & Co., Detroit.

Glaseptic Ampoules Sodium Cacodylate-P. D. & Co. (for Intravenous Use), 0.45 Gm. (7 grains), 5 cc.
Prepared by Parke, Davis & Co., Detroit.

Glaseptic Ampoules Sodium Cacodylate-P. D. & Co. (for Intravenous Use), 1 Gm. (15½ grains), 10 cc.
Prepared by Parke, Davis & Co., Detroit.

SOLARSON.—Solution Chlorarsenol, 1 per cent.—A 1 per cent solution of ammonium heptenchlorarsonate $(CH_3CH_2)_4$ $CCl:CH.AsO.OH.ONH_4)$, rendered isotonic by the addition of sodium chloride. Solarson contains from 0.255 to 0.275 Gm. of arsenic (As) in 100 cc.

Actions and Uses.—In experiments on rabbits the toxicity of solarson computed on the basis of its arsenic content, was found to be somewhat less than that of arsenic acid (H_3AsO_4) when given intravenously or subcutaneously; in dogs it was about the same. Repeated daily subcutaneous injections of an amount of solarson equivalent to 0.002 Gm. arsenic per kilogram was well tolerated by rabbits. An experiment on a dog showed that after the subcutaneous administration of a dose of solarson corresponding to 0.02 Gm. arsenic, the urine collected for twenty-four hours after the injection contained 0.0052 Gm. of arsenic and the feces in forty-eight hours 0.0012 Gm.: this is taken to show that the arsenic of solarson is readily liberated in the system and is well utilized. It is claimed that solarson has an advantage over the cacodylates, in that its arsenic is better utilized, and over the arsenilates in that subcutaneous and intramuscular injections produce less pain and are less liable to produce toxic effects.

Solarson is used as a means of obtaining arsenic effects in the treatment of anemia, chlorosis, malaria, neuroses and dermatoses.

Dosage.—From 1 to 2 cc. subcutaneously or intramuscularly.

Manufactured by the Bayer Co., Inc., Rensselaer, N. Y. (Winthrop Chemical Co., Inc., New York, distributor). U. S. patent 1,201,692 (Aug. 17, 1916; expires 1933). U. S. trademark 110,626.

Solarson Ampules, 1.2 cc.

Solarson is prepared by neutralization of heptenchlorarsonic acid with ammonium hydroxide and dilution with sufficient water to produce a 1 per cent solution of ammonium heptenchlorarsonic acid; sufficient sodium chloride is added to render the solution isotonic.

The heptenchlorarsonic acid used in the preparation of solarson responds to the following tests: It melts at 114 to 115 C. and contains 29.21 per cent of arsenic (As).

To determine the arsenic content of solarson, treat about 1 Gm. of solarson, accurately weighed, with 5 cc. of arsenic-free nitric acid and 5 cc. of arsenic-free sulphuric acid. Boil the mixture until white fumes appear; allow to cool and add 50 cc. of water and boil for five minutes. Allow the liquid to cool and make it up to 100 cc. with distilled water. Add 50 cc. of this liquid in portions to a generating Marsh apparatus. Collect the arsenic in a weighed arsenic tube 15 cm. long, heated to redness in two places and cooled in two other places by water-soaked wicks. Continue the collection of the arsenic for six hours, cool the arsenic tube and weigh it. The arsenic found in the solarson is not less than 0.255 Gm. nor more than 0.275 Gm. per hundred cubic centimeters.

TRYPARSAMIDE. — Sodium *N*-phenylglycinamide-*p*-arsonate. — $[(NH_2COCH_2NH).C_6H_4.(AsO.OH.ONa)]_2.H_2O$. — Tryparsamide contains 24.6 per cent of arsenic in organic combination.

Actions and Uses.—Tryparsamide was first used as a trypanocidal agent especially in the treatment of trypanosomiasis due to *T. gambiense* but is now used almost exclusively in the treatment of certain cases of syphilis of the central nervous system.

Tryparsamide has some spirocheticidal activity and has an unusual power of therapeutic penetration, especially in case of the central nervous system. The best results seem to have been obtained in patients with early paresis; it is estimated that perhaps from 40 to 50 per cent of such cases have shown varying degrees of symptomatic improvement. Tabetic affections have responded less satisfactorily, and patients with general paresis with advanced mental and physical deterioration have shown little or no improvement; on the other hand, the drug may hasten the progress of the disease in such cases. Its use is considered to be contraindicated in forms of syphilis other than that of the central nervous system, and it is held by some that it should be used in cerebrospinal syphilis only in cases that have failed to respond favorably to the arsphenamines. Mercury is frequently used in conjunction with the tryparsamide.

The toxic effects of tryparsamide resemble those of other pentavalent arsenic compounds; the worst of these is the tendency to produce amblyopia, but cases of jaundice have also been reported. Before using the drug, careful consideration should be given to the frequent production of visual injury, which may be serious and permanent. This caution is especially important if the neurosyphilis has involved the optic nerve. The eyeground fields should always be mapped out before its use is made. Sometimes after one or two injections the patient will complain of blurred vision for a few days. Generally if treatment is discontinued for a week or so and then the injections are reinstituted, there will be no further difficulty. The drug is said to "have no virtues in ophthalmic syphilis."

Dosage. — From 1.0 to 3.0 Gm. for adults, depending on the purpose for which the drug is used. In general, the dose should not exceed 0.04 to 0.05 Gm. per kilogram of body weight, and such doses should not be repeated at intervals of less than one week. Tryparsamide may be administered subcutaneously, intramuscularly or intravenously, though the intravenous administration is generally employed. The drug is dissolved in sterile water or physiological solution of sodium chloride. Tryparsamide should never be administered by mouth.

Manufactured by Merck & Co., Inc., Rahway, N. J., under U. S. patents 1,280,119, 1,280,120, 1,280,121, 1,280,122, 1,280,123, 1,280,124 and 1,280,126 (Sept. 24, 1918; expires 1935) by license of the Rockefeller Institute for Medical Research. U. S. trademark 186,022.

Tryparsamide occurs as a colorless, odorless crystalline powder (*distinction from arsphenamine compounds*). It is freely soluble in water, forming a solution neutral to litmus. It is insoluble or only slightly soluble in alcohol, ether, chloroform and benzene.

Treat the solution resulting from the assay with sulphuric acid and a slight excess of sulphur dioxide solution and boil until the odor of the latter is dispelled, then pass in hydrogen sulphide: a yellow precipitate forms, soluble in ammonium carbonate. To 1 cc. of a solution (1 in 10) add 1 cc. of diluted hydrochloric acid: a precipitate of phenyl glycinamide arsonic acid forms (*distinction from arsphenamine and sodium cacodylate*); further addition of diluted hydrochloric acid (2 to 3 cc.) does not entirely dissolve the precipitate, but addition of 2 cc. of strong hydrochloric acid dissolves the precipitate. Dissolve 0.5 Gm. in 5 cc. of water, add 3 cc. of sodium hydroxide solution (20 per cent) and boil: the characteristic odor of ammonia is detected. To 1 cc. of a solution (1 in 10) add 1 cc. of calcium chloride solution: a precipitate of microscopic, wedge-shaped prisms forms gradually. To 1 cc. of a solution (1 in 10) add 1 cc. of magnesia mixture: no precipitate forms in the cold (*arsenate or phosphate*); but, on warming the mixture, a precipitate forms. To 5 cc. of a 1 in 10 solution, add 0.3 cc. of sodium nitrite solution, 10 per cent, cool in ice water and add 5 cc. of diluted hydrochloric acid followed by a solution containing betanaphthol 5 per cent and sodium hydroxide 10 per cent: no red color is produced (*arsanilic acid*). To 1 cc. of tryparsamide solution (1 in 10) add 0.2 cc. of ferric chloride solution: no blue coloration is formed (*arsphenamine compounds*), but a brown precipitate develops, which dissolves on further addition of ferric chloride solution. To 1 cc. of solution (1 in 10) add 1 cc. of silver nitrate solution: a precipitate of thin microscopic needles is formed.

When dried to constant weight at 100 C., it loses not more than 3.5 per cent nor less than 2.5 per cent in weight (*water of hydration*).

Transfer about 0.2 Gm. of tryparsamide accurately weighed and previously dried at 100 C. to constant weight to a 150 cc. Erlenmeyer flask and add 5 cc. of concentrated sulphuric acid; rotate the contents of the flask to wet thoroughly the tryparsamide, then add 1 cc. of fuming nitric acid and heat the flask on a hot plate for one hour at a temperature of approximately 250 C. Remove the flask from the hot plate, cautiously add 0.5 cc. more of fuming nitric acid, and heat again for five minutes; allow to cool slightly and add, in several portions, 1 to 2 Gm. of solid ammonium sulphate, agitating the contents of the flask until the nitrogen has escaped. Transfer the cool solution with the aid of water to a 500 cc. Erlenmeyer flask and add enough water to make the total volume about 100 cc.; add potassium iodide, 1 Gm., and gently boil until the volume is reduced to about 40 cc.; cool, add tenth-normal sodium thiosulphate until the tint of iodine disappears; dilute with about 150 cc. of cold water, add sodium hydroxide solution, 20 per cent, until the solution is faintly alkaline to litmus; then add diluted sulphuric acid to render it slightly acid. Finally, add 20 cc. of a cold saturated sodium bicarbonate solution and titrate with tenth-normal iodine, using starch as indicator at the end. Each cubic centimeter of tenth-normal iodine corresponds to 0.003748 Gm. of arsenic. The amount of arsenic in the dried specimen should not be more than 25.5 per cent nor less than 25.1 per cent.

To determine the toxicity of tryparsamide, 0.75 Gm. of tryparsamide per kilogram of body weight in an aqueous solution, the concentration of which does not exceed 10 per cent is injected intravenously into well nourished, adult, male rabbits. Three out of five rabbits survive without serious intoxication. Young or old animals and animals that are either poorly nourished or abnormally fat, are less tolerant and should not be used for toxicity determinations.

ATROPINE DERIVATIVES AND ANALOGUES

Synthetic Mydriatics

The usefulness of atropine is somewhat diminished by the fact that it affects, simultaneously, so many organs; on the eye its effects continue much longer than is, in many cases, desirable. Many attempts have been made to secure drugs of the atropine type with more specific actions or such as have a more transitory effect upon the eye. One of these drugs (homatropine) is a synthetic alkaloid analogous to atropine, the only difference being that it contains mandelic acid instead of tropic acid in combination with tropine; eucatropine is a combination of mandelic acid and a base similar to that contained in beta-eucaine.

EUCATROPINE.—Eucatropina.—Euphthalmine.—Phenylglycolymethylvinyldiacetonalkamine Hydrochloride.—$C_5H_6N(CH_3)_4(C_6H_5CHOH.COO)HCl$ = the 1,2,6,6-tetramethyl-4-mandeloxypiperidine hydrochloride. Eucatropine was first introduced as euphthalmine.

Actions and Uses—Eucatropine produces prompt mydriasis free from anesthetic action, pain, corneal irritation, or increase in intra-ocular tension. It has little or no effect on accommodation, and such effect as it has disappears more rapidly than that of atropine, cocaine, homatropine, etc. In its effects on the general system, eucatropine very closely resembles atropine. It is useful as an aid in ophthalmoscopic examinations in place of atropine, homatropine, etc.

Dosage.—From 2 to 3 drops of from a 5 to a 10 per cent solution, according to the age of the patient and the nature of the case, are instilled into the eye.

Eucatropine is a white, granular, odorless powder; permanent in the air. It is very soluble in water; freely soluble in alcohol and chloroform; insoluble in ether. Eucatropine does not melt below 183 C. The aqueous solution of eucatropine (1 in 50) is clear and colorless and is neutral to litmus.

Aqueous solutions of eucatropine (1 in 50) are precipitated by sodium carbonate solution, potassium mercuric iodide solution, iodine solution, picric acid solution and many other reagents for the alkaloids. Add a few drops of nitric acid to about 0.005 Gm. of eucatropine, evaporate the mixture to dryness on a water bath, cool the residue and add a few drops of alcoholic potassium hydroxide solution together with a fragment of potassium hydroxide: no violet color results (*distinction from atropine, scopolamine or hyoscyamine*).

Incinerate about 0.5 Gm. of eucatropine, accurately weighed: the ash amounts to not more than 0.1 per cent.

Dissolve about 1 Gm. of eucatropine, accurately weighed, in 10 cc. of water, make alkaline with ammonia water, shake with successive portions of ether until extraction is complete, washing the ether layer each time with water and adding the washings to the original solution before the next extraction; allow the solvent to evaporate spontaneously, dry the residue to constant weight at 80 C. and weigh: the residue of eucaptropine base is not less than 86 per cent.

Recrystallize the free base obtained as above from petroleum ether: the crystals do not melt below 111 C.

HOMATROPINE HYDROCHLORIDE. — Homatropinae Hydrochloridum.—$C_{16}H_{21}O_3NHCl$.—The hydrochloride of the alkaloid homatropine, obtained by the condensation of tropine and mandelic acid.

Actions and Uses.—Homatropine hydrochloride is given for the same indications as the hydrobromide.

Dosage.—It is applied to the eye in 1 per cent solution.

Homatropine hydrochloride occurs as small white crystals, soluble in water and alcohol and melting at from 216 to 217 C.

The color test for the identification of homatropine hydrochloride and those showing the absence of impurities should agree with those described in the U. S. Pharmacopeia under homatropine hydrobromide.

Homatropine Hydrochloride-Merck.—A brand of homatropine hydrochloride-N. N. R.

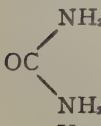
Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

Homatropine Hydrochloride-Roche.—A brand of homatropine hydrochloride-N. N. R.

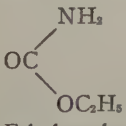
Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J.). No U. S. patent or trademark.

BARBITAL AND BARBITAL COMPOUNDS

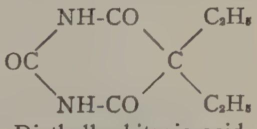
Barbital (diethylbarbituric acid), which was introduced under the name of "veronal," is chemically related to urea and the carbamate hypnotics:



Urea



Ethyl carbamate
(Urethane)



Diethylbarbituric acid
(Barbital)

The ethyl groups may be replaced by other alkyl or aryl radicals to form a large number of derivatives. Compounds in which the ethyl group of barbituric acid is replaced by the normal butyl group (neonal), the cyclo-hexenyl group (phanodorn), the phenyl group (phenobarbital, luminal) are accepted for N. N. R. These "acids" are only sparingly soluble in water; but freely soluble compounds are formed by substitution of sodium or calcium for the hydrogen of one of the NH groups of such to make sodium barbital (soluble barbital), sodium phenobarbital (luminal sodium) and calcium ethylisopropyl barbituric acid (ipral) all of which are accepted and described in N. N. R.

Actions and Uses.—Barbital and its derivatives are effective sedatives and hypnotics, and are used as such in simple insomnia, hysteria, neurasthenia, thyroid disease, chorea, in epilepsy in the intervals between the seizures, mental disturbances and in impending delirium tremens. They also augment the action of analgesics such as amidopyrin, acephenetidin and acetylsalicylic acid, and they are used in combination with these analgetics for the relief of pain, especially of neuralgic character.

They are decidedly more actively hypnotic, and somewhat more analgetic than chloral hydrate; they do not produce local irritation and the taste is not disagreeable. The margin between the ordinary therapeutic dose and the toxic dose is somewhat wider than that with chloral hydrate, and small therapeutic doses have little effect on the blood pressure and respiration. Several of the derivatives of barbital are more actively hypnotic than the parent substance and may be preferred, especially as a sedative; but there is no satisfactory evidence that the margin between the therapeutic and toxic doses of these derivatives is wider than in the case of barbital itself. The action is somewhat slower than with chloral hydrate, but more rapid than with sulphonmethane. In the absence of pain, small doses usually induce sleep within half an hour. The sleep lasts for four to eight hours, varying with individuals, with the drug used and with the dose. The patient generally wakens refreshed, but occasionally there are lassitude, vertigo, headache, nausea and diarrhea on the following day even after moderate doses. Skin eruptions are sometimes observed. Fatal collapse (by peripheral paralysis of the blood vessels) has occurred after relatively small doses. Toxic doses cause lowered body temperature, depression of the respiration and circulation, and feeble heart beat. There is long-continued stupor, sometimes interrupted by excitement. The condition has been confused with uremia, epidemic encephalitis and opium poisoning. The slower the excretion of the various members of this group, the more lasting is the action, and with very slow excretion ordinary doses may produce cumulative toxic effects after some time. It is therefore safer to intermit the administration at least weekly. Continued use may lead to habitual addiction.

BARBITAL.—Barbitalum.—For description see the U. S. Pharmacopeia and Useful Drugs.

Actions and Uses.—See the preceding article, Barbital and Barbital Compounds. Barbital is quickly absorbed, especially when it is given in solution. Small doses induce sleep apparently with little other effect, and are relatively safe; but fatalities have followed its indiscriminate use.

Dosage.—As hypnotic, 0.5 Gm. (8 grains), best prescribed in the form of powder to be given in hot fluid, such as hot milk, half an hour or an hour before bed time. Pills or tablets should be crushed before swallowing, to insure absorption. From 0.1 to 0.15 Gm. (1½ to 2 grains) are used with analgetics for the relief of pain.

Veronal.—A brand of barbital-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent 782,739 (Feb. 14, 1905; expired). U. S. trademark 40,115.

Veronal Tablets, 5 grains.

Elixir of Veronal: Each fluid drachm contains veronal 2 grains in a menstruum containing alcohol 33.5 per cent.

DIAL-CIBA.—Diallylbarbituric acid.—Diallylmalonylurea. —2,4,6-trioxy-5-diallylpyrimidin.—
$(C_3H_5)_2\underline{C\ CONH\ CONH\ CO}$. Dial-Ciba differs from barbital (diethylbarbituric acid) in that both of the ethyl groups of the latter are replaced by allyl groups.

Actions and Uses.—The actions and uses of dial-Ciba are essentially similar to those of barbital, but dial-Ciba is more active than barbital and it is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as a hypnotic. Therapeutic doses act on the higher cerebral centers and exert no injurious action on the heart or circulation. The hypnotic action is induced within one-half to one hour.

Dosage.—As a sedative: 0.02 to 0.04 Gm. (⅓ to ¾ grain) two or three times daily. As a hypnotic: 0.1 to 0.3 Gm. (1½ to 4½ grains) one-half to one hour before sleep is desired.

Manufactured by the Society of Chemical Industry in Basle, Switzerland (Ciba Company, Inc., New York, Distributor). U. S. patent 1,042,265 (Oct. 22, 1912; expired). U. S. trademark 98204 and 126088.

Tablets Dial-Ciba, 0.1 Gm. (1½ grains).

Elixir Dial-Ciba: Each 4 cc. (1 fluidrachm) contains 0.05 Gm. (¾ grain) in a menstruum containing alcohol 25 per cent.

Dial-Ciba occurs as a fine, white, crystalline powder, with a slightly bitter taste; completely soluble in alcohol and ether; very slightly soluble in cold water; insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Dial-Ciba melts at 171-173 C.

Place approximately 0.3 Gm. dial-Ciba in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of mercuric chloride solution: a white precipitate results, soluble in 10 cc. of ammonia water; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in 5 cc. of ammonia water.

Boil 0.5 Gm. with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia. Dissolve 0.1 Gm. in 1 cc. of sulphuric acid: the liquid assumes a yellow color, changing slowly to a brownish-red, finally to a dark red. Place 1 Gm. in a 25 cc. glass stoppered cylinder, add 10 cc. of water, shake for one minute, filter through paper and divide into two portions; to one portion add 0.5 cc. of a saturated bromine water: an immediate discoloration occurs; to the other portion add 0.1 cc. of tenth-normal potassium permanganate: a yellow color appears immediately.

Boil 0.5 Gm. of dial-Ciba with 50 cc. of water for two minutes: no odor develops; cool and filter: separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulphate*); no coloration or precipitation on saturation with hydrogen sulphide (*salts of heavy metals*).

Incinerate about 1 Gm. of dial-Ciba, accurately weighed: the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol; dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide solution, using thymolphthalein as an indicator: the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent, nor more than 101.5 per cent of diallylbarbituric acid.

SOLUBLE BARBITAL.—For description see the U. S. Pharmacopeia under Barbitalum Solubile.

Actions and Uses.—The same as those of barbital, but it is claimed that this drug acts more rapidly on account of its greater solubility. Because of its solubility, administration by rectal injection and also subcutaneous injection has been proposed.

Dosage.—The same as that of barbital. It should be administered in aqueous solution.

Veronal-Sodium.—A brand of soluble barbital-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent 782,739 (Feb. 14, 1905; expired). U. S. trademark 40,115.

Veronal-Sodium Tablets, 5 grains.

PHENOBARBITAL.—**Phenobarbitalum.**—For description see the U. S. Pharmacopeia and Useful Drugs.

Actions and Uses.—The introduction of the phenyl group increases the hypnotic and sedative action of phenobarbital over that of barbital. The toxicity appears to be increased in about the same ratio. The sleep may be preceded by a period of excitement. Moderately large therapeutic doses sometimes cause severe circulatory depression. The formation of a habit has been reported.

Phenobarbital has a sedative action on respiration, lessening the frequency of breathing. It kills by respiratory paralysis. It is eliminated by the kidneys, a certain portion being probably decomposed in the organism. No gastric disturbances have been observed.

Phenobarbital is used as a useful hypnotic in nervous insomnia and conditions of excitement of the nervous system; its chief use in this field is as a sedative and antispasmodic in the treatment of epilepsy, in which it lessens the frequency and severity of seizures. Its use as a sedative has also been proposed in chorea, neurasthenia, cardiac and gastric neuroses, climacteric disorders, dysmenorrhea, exophthalmic goiter, and preoperative and postoperative cases; but it should be remembered that the drug has no curative action in such conditions.

Dosage.—From 0.015 to 0.2 Gm. (¼ to 3 grains) increased if necessary to 0.6 Gm. (10 grains). The average dose is 0.1 Gm. (1½ grain). A maximum dose of 0.6 Gm. (10 grains) should not be exceeded.

Luminal.—A brand of phenobarbital-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent 1,025,872 (May 7, 1912; expires 1929). U. S. trademark 87,327.

Elixir of Luminal: Each 4 cc. (one fluidrachm) contains 0.0162 Gm. (¼ grain) in a menstruum containing alcohol 20 per cent.

Luminal Capsules, 1½ grains.

Luminal Tablets, ¼ grain.

Luminal Tablets, ½ grain.

Luminal Tablets, 1½ grains.

LUMINAL-SODIUM. — Phenobarbital Sodium. — Sodium Phenylethylbarbiturate.—Luminal Soluble. — $Na(C_{12}H_{11}N_2O_3)$. —The monosodium salt of phenylethylbarbituric acid.

Actions and Uses.—The same as those of phenobarbital.

Dosage.—For hypodermic injection, luminal-sodium is used in the form of 20 per cent solution, prepared by dissolving the salt in boiled and cooled distilled water; 2 cc. (30 minims) of the solution contain 0.4 Gm. (6 grains) of luminal-sodium. The dose of luminal-sodium is 10 per cent greater than that of luminal.

Luminal-sodium may be given hypodermically in doses of 0.1 to 0.3 Gm. (1½ to 5 grains).

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent 1,025,872 (May 7, 1912; expires 1929). U. S. trademark 87,327.

Ampules Luminal-Sodium (Powder), 2 grains.

Luminal Sodium Tablets, 1½ grains.

Luminal-sodium is a white, hygroscopic powder; very soluble in water; soluble in alcohol; practically insoluble in ether and chloroform. An aqueous solution of luminal-sodium has an alkaline reaction to litmus. On long standing or prolonged boiling of the aqueous solution, 1 molecule of carbon dioxide is liberated and phenylethylacetyl urea is precipitated; after recrystallization from dilute alcohol this substance melts at 147 C.

Incinerate about 0.5 Gm. of luminal-sodium: the residue responds to tests for sodium carbonate. Acidify an aqueous solution of luminal-sodium with hydrochloric acid and shake with ether. Evaporate the solvent: the residue responds to tests for luminal (which see).

One gram of luminal-sodium dissolves without residue in 20 cc. of alcohol (*distinction from barbital sodium, which requires more than 500 cc. of alcohol for solution*).

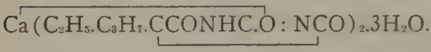
Dry about 1 Gm. of luminal-sodium, accurately weighed, to constant weight over sulphuric acid: the loss does not exceed 5 per cent.

Dry about 1 Gm. of luminal-sodium, accurately weighed, to constant weight at 140 C.: the loss does not exceed 5 per cent.

Dissolve about 1 Gm. of luminal-sodium, accurately weighed, in water, acidify the solution with sulphuric acid, shake the solution with successive portions of ether, allow the solvent to evaporate spontaneously, dry the residue to constant weight at 80 C. and weigh: the residue amounts to not less than 86 per cent of the weight taken.

Add 5 cc. of diluted sulphuric acid to the aqueous solution remaining from the preceding determination, evaporate the solution in a weighed platinum dish on a water bath, heat cautiously until the excess of sulphuric acid has been volatilized, add about 0.5 Gm. of ammonium carbonate and heat to constant weight: the weight of sodium sulphate obtained corresponds to not less than 8.5 per cent of sodium.

IPRAL.—Calcium ethylisopropylbarbiturate.—



$Ca(C_2H_5.C_3H_7.CCONHC.O:NCO)_2.3H_2O$. The calcium salt of ethylisopropylmalonyl urea.

Actions and Uses.—Ipral has the therapeutic properties of barbituric acid. It is soluble in water and is absorbed promptly. It is claimed that it is excreted rapidly, but some action commonly persists for twenty-four hours. In therapeutic doses it affects the higher cerebral centers almost exclusively, and such doses exert no perceptible effect on the heart or circulation directly.

Ipral is used as a hypnotic to combat restlessness, irritability and sleeplessness. It is claimed that tolerance to ipral is not developed readily, but that its action is so persistent that a patient frequently sleeps on the night succeeding that when the hypnotic was administered.

Dosage.—From 0.12 to 0.25 Gm. (2 to 4 grains) followed by a cupful of hot water, tea or milk. Ipral is marketed in the form of 2 grain tablets, only.

Manufactured by E. R. Squibb & Sons, New York. U. S. patent 1,255,951 (Feb. 12, 1918; expires 1935); 1,576,014 (March 9, 1926; expires 1943). U. S. trademark 208,813.

Ipral Tablets, 2 grains.

Ipral occurs as a white, crystalline, odorless powder, with a slight bitter taste. It is soluble in about 40 parts of water at 25 C.; insoluble in alcohol. An aqueous solution is alkaline in reaction to litmus.

Add 0.2 Gm. to 20 cc. of water, acidify with 5 cc. diluted hydrochloric acid, filter, make filtrate ammoniacal, then add 2 cc. of ammonium oxalate solution: a precipitate forms, insoluble on addition of acetic acid in excess, but soluble on the addition of hydrochloric acid. Wash well the residue from the foregoing with water, dry at 100 C.: the melting point should be from 200 to 203 C. To 0.05 Gm. of residue add 2 cc. sodium hydroxide solution: the residue dissolves. Place 2 Gm. in a glass stoppered flask, treat with 25 cc. of carbon dioxide free water and agitate occasionally over a period of two hours; by decantation separate the insoluble material, transfer the insoluble residue to a test tube, treat with diluted sulphuric acid and pass the emitted gases into 20 cc. of barium hydroxide solution: not more than a barely perceptible turbidity should result (*limit of carbonate*). Dry about 1 Gm., accurately weighed, to constant weight at 100 C.: the loss does not exceed 12 per cent. Transfer about 1 Gm., accurately weighed, to a glass stoppered cylinder, add 50 cc. of ether, stopper and shake the contents for five minutes; decant the supernatant liquid through filter paper, and repeat, using 25 cc. and 15 cc. portions, respectively, of ether; evaporate the filtrate to dryness in a tared beaker and dry to constant weight at 100 C.: the residue should not weigh more than 4 per cent (*limit of uncombined ethylisopropyl barbituric acid*). Dissolve about 1 Gm., accurately weighed, in water, acidify with 10 cc. of diluted hydrochloric acid, extract with five successive portions of ether, allow the solvent to evaporate spontaneously, dry the residue to constant weight at 100 C., and weigh: the weight of ethylisopropyl barbituric acid is not less than 78.5 per cent, nor more than 83.0 per cent. Ignite about 1 Gm., accurately weighed, cool, treat the residue with 5 cc. diluted hydrochloric acid, transfer to a 250 cc. beaker, add 25 cc. water and ammonia water until ammoniacal, warm, add 20 cc. boiling ammonium oxalate solution, boil and allow to stand over night; collect the precipitate on an ashless filter paper, wash with diluted ammonia water (1 part of ammonia water to 5 parts of water), transfer the precipitate to a platinum crucible, and ignite to constant weight: the weight of calcium oxide corresponds to not less than 8.0 per cent nor more than 8.5 per cent calcium.

NEONAL. — *N*-Butylethylbarbituric acid.—*N*-Butylethylmalonylurea. — 2,4,6-trioxy-5-*N*-Butylethylpyrimidin. — $NC_4H_9(C_2H_5)\underline{C\ CONH\ CONHC}\ O$.—Neonal differs from barbital (diethylbarbituric acid) in that one of the ethyl groups of the former is replaced by a normal butyl group.

Actions and Uses.—The actions and uses of neonal are essentially similar to those of barbital, but it is about three times as active as the latter; hence it is used in correspondingly smaller doses. It is claimed that it exerts a sedative action to an exceptional degree, and that it is useful therefore in high nervous tension, neuroses and other conditions in which a sedative is required. It has the property in common with other barbituric acid derivatives of augmenting the action of analgesics such as amidopyrin, acetphenetidin and acetylsalicylic acid.

Dosage.—From 0.05 to 0.4 Gm. (¾ to 6 grains). For mild insomnias 0.05 to 0.1 Gm. (¾ to 1½ grains) is stated ordinarily to produce sleep. A dose of 0.4 Gm. (6 grains) is the maximum dose which should be required in the course of twenty-four hours, administered in divided doses.

Manufactured by the Abbott Laboratories, North Chicago, Ill., under U. S. patent 1,609,520 (Dec. 7, 1926; expires 1943) by license of Les Establissements Poulenc Freres. U. S. trademark 175,580.

Neonal Tablets, 0.1 Gm.

Neonal occurs as a white, crystalline, odorless powder, with a slightly bitter taste; readily soluble in alcohol, about 1 in 5, and ether about 1 in 10; very slightly soluble in cold water; insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. It melts at 124-127 C. It is stable in air.

Place 0.3 Gm. in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of mercuric chloride solution: a white precipitate results, soluble in 10 cc. of ammonia water; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in 5 cc. of ammonia water. Boil 0.5 Gm. with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia.

Dissolve 0.1 Gm. in 1 cc. of sulphuric acid: the solution is colorless (*readily carbonizable substances*). Boil 0.5 Gm. with 50 cc. water for two minutes: no odor develops; cool and filter; separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulphate*); no coloration or precipitation on saturation with hydrogen sulphide (*salts of heavy metals*).

Incinerate about 1 Gm. accurately weighed: the residue does not exceed 0.1 per cent.

Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide solution, using thymolphthalein as an indicator: the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of *N*-Butylethylbarbituric acid.

PHANODORN.—Cyclobarbital.—Cyclohexenyl ethyl barbituric acid. — Δ^1-cyclohexenyl ethyl malonyl-urea. — 2,4,6, trioxy-5-cyclo-hexenyl-ethyl-pyrimidin.—

$\underbrace{CH_2CH_2CH_2CH_2CH}:C.(C_2H_5).C\underbrace{CONHCONHCO}$. Phanodorn differs from barbital (diethyl-barbituric acid) in that one of the ethyl groups of barbital is replaced by a cyclohexenyl group.

Actions and Uses.—The actions and uses of phanodorn resemble those of barbital. It is eliminated more rapidly than barbital; hence the action is not so lasting. This is an advantage when it is used merely to put one to sleep where sleep will then continue without its further action. It is used mainly for its sedative action in nervous insomnia, neurasthenia, psychoses, and various types of insomnia. It probably augments the action of analgesics such as amidopyrine, as other barbituric acid derivatives do.

Dosage.—For the mildest type of simple insomnia, 0.1 Gm. (1½ grains) or ½ tablet. Intractable or obstinate insomnia, from 0.2 to 0.4 Gm. (3 to 6 grains) or one to two tablets. The larger dose should not be repeated within less than twelve hours. The average dose is 0.2 Gm. (3 grains), or one tablet.

Manufactured by the Bayer Company, Inc., Rensselaer, N. Y. (Winthrop Chemical Company, Inc., New York, distributor). U. S. patent applied for.

Phanodorn Tablets, 3 grains.

Phanodorn occurs as a white, crystalline, odorless powder, with a bitter taste; readily soluble in alcohol, about 1 in 5, and ether, about 1 in 10; very slightly soluble in benzene and cold water. A saturated aqueous solution is acid to litmus paper. It melts at 171-174 C.

Dissolve 0.1 Gm. in 1 cc. of sulphuric acid: the liquid assumes a yellow color, changing quickly to orange, and finally to red. Place 0.3 Gm. in a 25 cc. glass stoppered cylinder, add 1 cc. normal sodium hydroxide solution and 5 cc. water, shake the contents for one minute, filter through paper and divide into two portions: the solutions yield a white precipitate with 1 cc. of mercuric chloride solution, soluble in 5 cc. of ammonia water; the solution yields a white precipitate with 2 cc. of silver nitrate solution, soluble in 5 cc. of ammonia water. Boil 0.5 Gm. with 5 cc. of a 20 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia.

Boil 0.5 Gm. with 50 cc. of water for two minutes; no odor develops; cool and filter: separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulphate*); no coloration or precipitation on saturation with hydrogen sulphide (*salts of heavy metals*).

Incinerate about 1 Gm. accurately weighed: there is not more than 0.01 per cent residue.

Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide solution using thymolphthalein as an indicator: the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent.

BARIUM SULPHATE.—For description see the U. S. Pharmacopeia under Barii Sulphas.

Actions, Uses and Dosage.—Barium sulphate for roentgen-ray work, being freed from soluble barium and other salts, passes through the system unchanged and because of this is used in taking roentgenograms of the stomach and of the intestines.

For the Roentgen-Ray Examination of the Stomach.—The evening before the examination, the patient receives 1 fluidounce of castor oil. In the morning an ordinary portion of wheat-meal porridge, with which 2 ounces of barium sulphate has been well mixed, together with a little sugar and cream, is administered by mouth. The patient is then directed to abstain from further food. The examination is made six hours later.

For the Roentgen-Ray Examination of the Colon.—An enema consisting of 16 ounces of mucilage of acacia, 3 pounds of condensed milk, and 8 ounces of barium sulphate is warmed to body temperature and injected into the rectum from a height of from 3 to 6 feet (90 to 180 cm.). The examination is made with a fluoroscope while the injection is passing into the rectum.

I-X Barium Meal.—A mixture of barium sulphate U. S. P., 85 per cent; native aluminum silicate, 10 per cent; malted milk (malt extract-milk powder), 5 per cent; with a trace of saccharin.

Actions and Uses.—I-X barium meal is used for roentgen-ray examinations.

Dosage.—I-X barium meal may be administered orally or by rectum. From 90 Gm. to 120 Gm. (3 to 4 ounces) are mixed with each 250 cc. (8 fluidounces) of water and agitated thoroughly.

Manufactured by the Industrial X-Ray Research Laboratories, St. Louis (Dick X-Ray Company, St. Louis, distributor). U. S. patent and trademark applied for.

Skiabaryt for Oral Administration: A mixture of barium sulphate-U. S. P., 75 to 85 per cent admixed with sugar, tragacanth, vanillin, cinnamon and cacao.

Dosage.—Triturate 150 to 200 Gm. (5 to 6.5 ounces) with cold water added gradually to form a smooth, thin paste; then add warm water gradually until the mixture measures 500 cc. (16 fluidounces). The mixture is than ready for drinking.

Merck & Co., Inc., New York, distributor. No U. S. patent. U. S. trademark 165,022.

Skiabaryt for Rectal Administration: A mixture of barium sulphate-U. S. P., 75 to 85 per cent admixed with sugar, tragacanth, vanillin and cinnamon.

Dosage.—Mix 200 Gm. (6.5 ounces) with cold water to form a smooth paste; then add warm water with stirring until the mixture has acquired a fairly fluid consistency. It is then ready for administration through the irrigator.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent. U. S. trademark 165,022.

BENZENE, MEDICINAL.—Benzenum Medicinale.—Medicinal Benzol.—Crystallizable Benzol.—C_6H_6.—A liquid consisting almost entirely of benzene (cyclohexatriene).

Actions and Uses.—When swallowed, this drug usually produces a sensation of burning in the stomach. Benzene is a narcotic which, when swallowed or inhaled, produces vertigo, delirium and tonic convulsions followed by deep sleep; the ingestion of 30 cc. (1 ounce) of nearly pure benzene has proved fatal. In some cases of chronic poisoning, petechial spots, due to small hemorrhages, have been observed. These spots have been attributed to fatty degeneration of the blood vessels. It produces leukocytosis followed by leukopenia with an occasional increased number of erythrocytes. Larger doses may produce an aplastic anemia. It has been stated that the aplastic anemia is due to a contamination of the drug with nitrobenzene or aniline. Benzene has been used occasionally on account of its narcotic properties and has also been used as an intestinal antiseptic. It is, however, rarely used for these purposes at the present time. It has been somewhat extensively used in the treatment of leukemia. Moderate doses cause a rapid destruction of the leukocytes, especially the lymphocytes. This action is accompanied by an improvement in the subjective symptoms and, in some cases, by a marked reduction in the size of the spleen. In many cases the lymphocytes have been reduced to the normal figure. In others the number of leukocytes has still remained high, although the size of the spleen was reduced. In many cases the improvement is such that an apparent cure is produced. However, a large number, if not all, of these patients relapse or succumb to the toxic action of the benzene. The administration of this drug should be stopped before the leukocytes are reduced to the normal level. Benzene has also been used in a few cases of Hodgkin's disease and in cases of polycythemia. The effect of benzene on the leukocytes is largely enhanced by the previous or simultaneous treatment with the roentgen ray. The value of benzene in leukemia is not established and caution against too large and too long-continued dosage should govern its employment.

Dosage.—From 0.5 to 1 cc. (8 to 15 minims) given four times a day. Medicinal benzene may be given in capsules or in an emulsion or may be administered by rectum. Frequent examinations of the blood should be made during the administration of medicinal benzene to determine when it is advisable to suspend the administration of the medicine.

Medicinal benzene is prepared by fractional distillation of the light oil of coal tar and is a colorless, mobile liquid, possessing a strong characteristic, but not disagreeable, odor and a burning taste. It has a specific gravity of from 0.881 to 0.885 at 15 C.

Medicinal benzene is insoluble in water but soluble in 90 per cent alcohol and in carbon disulphide; it is miscible with absolute alcohol and ether.

Medicinal benzene boils at from 79 to 82 C. It is inflammable and burns with a luminous and sooty flame. When cooled to 0 C., medicinal benzene solidifies. If cooled slowly it crystallizes in rhombohedral prisms, which melt at about 6 C. It is neutral to litmus. Medicinal benzene is not affected by cold sulphuric acid, but is soluble in fuming nitric acid, without liberating nitrous vapors. When poured into water the mixture separates and deposits oily globules of nitrobenzene, which can be identified by the odor. If 2 cc. of medicinal benzene be shaken with 0.5 cc. concentrated sulphuric acid and 1 drop of fuming nitric acid, no green or blue tint should be produced.

Benzene (Benzol)-Merck Medicinal, "C. P." Crystallizable.—A brand of benzene, medicinal-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

BENZYL COMPOUNDS

A pharmacologic investigation of opium alkaloids made a few years ago brought out the fact that drugs of the papaverine group tend to cause relaxation and inhibition of smooth muscle structures, and it was suggested that this action is dependent on the benzyl grouping in the papaverine molecule. This in turn suggested that possibly the same action might be secured by administering the benzyl radical in a simpler form than that in which it is contained in papaverine. A number of benzyl esters, such as benzyl acetate and benzyl benzoate, were therefore investigated. It was found that they lower the tonus of smooth muscle and at the same time are relatively nontoxic. To overcome the pungent taste of these liquid benzyl esters, insoluble solid benzyl compounds have been prepared, such as benzyl fumarate and benzyl succinate. In general, these have the same properties as the liquid benzyl esters, except that they act more slowly.

Based on this pharmacologic study, the use of the benzyl esters in medicine was proposed. They soon gained considerable vogue, and have been recommended in general as useful in a variety of pathologic conditions associated with spasm of the smooth muscle in hypertension, asthma, angina, dysmenorrhea, biliary and renal colic and similar disorders. Extensive clinical use of the benzyl esters does not seem to confirm the enthusiastic estimate of their early advocates.

The benzyl esters apparently give relief in a certain proportion of cases of dysmenorrhea. A small percentage of cases of angina and of intestinal colic appear to be benefited by their use. They have been found without effect in hypertension and they are probably without effect in asthma or renal or biliary colic.

BENZYL BENZOATE.—**Benzylis Benzoas.**—$C_6H_5COO.CH_2C_6H_5$.—The benzyl alcohol ester of benzoic acid. It contains not less than 95 per cent benzyl benzoate.

Actions and Uses.—See preceding article, Benzyl Compounds.

Dosage.—From 0.3 to 0.5 cc. (5 to 8 minims).

Benzyl benzoate is a colorless oily liquid above about 20 C. It is odorless, or has a faint aromatic odor, and a sharp burning taste. It is insoluble in water or glycerin but miscible in all proportions with alcohol, chloroform and ether. Benzyl benzoate boils at from 320 to 325 C. with partial decomposition. When ignited it burns with a very smoky flame. Specific gravity 1.09 to 1.13 at 15 C., 1.083 to 1.122 at 25 C.

Benzyl benzoate is neutral to litmus. It is readily saponified by alcoholic solution of potassium hydroxide. The solution obtained when neutralized yields a flesh-colored precipitate with ferric chloride solution, and upon acidulation a white crystalline precipitate of benzoic acid separates. This precipitate may be identified by extracting with ether and applying the usual tests for benzoic acid.

Ten cc. of benzyl benzoate should leave no weighable residue on evaporation and heating until all carbon is burned away.

To about 2 Gm. of benzyl benzoate, accurately weighed, add 25 cc. of half-normal alcoholic potassium hydroxide and heat the mixture to incipient boiling under a reflux condenser for one hour. To the cooled solution add phenolphthalein and titrate the excess potassium hydroxide with half-normal hydrochloric acid: the volume of half-normal potassium hydroxide used should indicate not less than 95 per cent benzyl benzoate.

Benzyl Benzoate-Abbott.—A brand of benzyl benzoate-N. N. R.

The Abbott Laboratories, North Chicago. No U. S. patent or trademark.

Elixir Benzyl Benzoate-Abbott: Composed of 20 per cent benzyl benzoate-Abbott, 70 per cent ethyl alcohol (95 per cent) flavoring, and water to make 100 per cent.

Dosage.—Twenty drops to 2 teaspoonfuls, well diluted with water or milk. May be repeated in from one-half to one hour.

Tablets Benzyl Benzoate-Abbott, 2 grains: Each contains benzyl benzoate-Abbott, 2 grains with charcoal as a vehicle.

Dosage.—From 2 to 5 tablets at intervals of one-half to one hour continued to effect (up to 20 grains). Follow each dose with a hot drink--water or milk.

Benzyl Benzoate-Fritzsche.—A brand of benzyl benzoate-N. N. R.

Fritzsche Brothers, Inc., New York. No U. S. patent or trademark.

Benzyl Benzoate-H. W. & D.—A brand of benzyl benzoate-N. N. R.

Hynson, Westcott and Dunning, Baltimore, Md. No U. S. patent or trademark.

Globules of Benzyl Benzoate-H. W. & D.: Each contains benzyl benzoate-H. W. & D., 5 minims, diluted with olive oil.

Sterile Ampules of Benzyl Benzoate-H. W. & D., 0.5 Cc.: One cc. contains benzyl benzoate-H. W. & D., 0.5 cc. diluted with olive oil. Each ampule contains more than 1 cc.

Solution of Benzyl Benzoate, Miscible-H. W. & D.: A solution of 20 Gm. of benzyl benzoate in 78 Gm. of ethyl alcohol to which is added 2 Gm. of powdered castile soap as an emulsifying agent.

Actions and Uses.—The same as those of benzyl benzoate.

Dosage.—From 1.5 to 2 cc. (20 to 30 minims): from 4 to 8 cc. (1 to 2 fluidrachms) may be administered when so prescribed.

Benzyl Benzoate-Mallinckrodt.—A brand of benzyl benzoate-N. N. R.

The Mallinckrodt Chemical Works, St. Louis, distributor. No U. S. patent or trademark.

Benzyl Benzoate-Merck.—A brand of benzyl benzoate-N. N. R.

Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

Benzyl Benzoate-Seydel.—A brand of benzyl benzoate-N. N. R.

Seydel Chemical Company, Jersey City, N. J. No U. S. patent or trademark.

BENZYL FUMARATE-ABBOTT.—Benzylis Fumaras.—Dibenzyl Fumarate.—$C_6H_5CH_2.OOC.CH:CH.COO.CH_2C_6H_5$.—It contains not less than 99 per cent of benzyl fumarate.

Actions and Uses.—See preceding article, Benzyl Compounds.

Dosage.—From 0.3 to 1.3 Gm. (5 to 20 grains).

Manufactured by the Abbott Laboratories, North Chicago. No U. S. patent or trademark.

Tablets Benzyl Fumarate, Abbott, 5 grains.

Benzyl fumarate is a white, crystalline solid; odorless; almost tasteless. It is almost insoluble in water; soluble in alcohol, ether and chloroform; also soluble in the fixed and volatile oils. It melts at 58.5 to 59.5 C. The solution of benzyl fumarate in chloroform (1 in 25) should be clear and colorless.

Boil about 2 Gm. of benzyl fumarate with 30 cc. of half-normal alcoholic sodium hydroxide in a reflux apparatus for 1 hour. Cool, filter, wash the precipitate with alcohol, dissolve the precipitate in the minimum quantity of warm water and acidify with concentrated hydrochloric acid. Recrystallize the residue once from a few cc. of hot water: the crystals of fumaric acid sublime without melting at a temperature above 200 C. To the alcoholic filtrate from the sodium fumarate add 25 cc. of water and boil until the alcohol is removed. Shake the alkaline solution twice with ether, using 10 cc. each time, and evaporate these extractions: the residue has the odor of benzyl alcohol. Add about 1 cc. of diluted sulphuric acid to 10 cc. of tenth-normal potassium permanganate, add 0.1 Gm. of benzyl fumarate and warm the mixture: the odor of benzaldehyde becomes perceptible. Shake 1 Gm. of finely divided benzyl fumarate with 100 cc. of water and filter; the filtrate should not be more than faintly acid to litmus paper and separate portions should not yield precipitates with barium chloride solution, silver nitrate solution or be colored violet by ferric chloride solution.

Incinerate about 1 Gm. of benzyl fumarate, accurately weighed: not more than 0.1 per cent of ash remains. Boil about 1 Gm. of benzyl fumarate, accurately weighed, for 1 hour in a reflux apparatus with 20 cc. of half-normal alcoholic sodium hydroxide solution, cool the solution, add a few drops of phenolphthalein solution, and titrate with half-normal hydrochloric acid until the disappearance of the pink color: the amount of half-normal sodium hydroxide consumed corresponds to not less than 99 per cent of benzyl fumarate.

BENZYL SUCCINATE.—Benzylis Succinas.—Dibenzyl Succinate. — $C_6H_5CH_2.OOC.CH_2.CH_2.COO.CH_2C_6H_5$. — The dibenzyl ester of succinic acid. It contains not less than 99 per cent of benzyl succinate.

Actions and Uses.—See preceding article, Benzyl Compounds.

Dosage.—0.3 to 1 Gm. (5 to 15 grains).

Tablets of Benzyl Succinate-H. W. & D.: Each contains benzyl succinate N. N. R., 5 grains.

Prepared by Hynson, Westcott & Dunning, Baltimore.

Benzyl succinate is a white, or faintly yellowish-white, crystalline powder; odorless; almost tasteless; permanent in the air.

Benzyl succinate is almost insoluble in water, soluble in alcohol, ether and chloroform; also soluble in the fixed and volatile oils.

Benzyl succinate melts at 45 C.

Boil about 2 Gm. of benzyl succinate with 30 cc. of half-normal alcoholic sodium hydroxide in a reflux apparatus for 1 hour. Cool, filter, wash the precipitate with alcohol, dissolve the precipitate in the minimum quantity of warm water, and acidify with concentrated hydrochloric acid. Recrystallize the residue once from a few cc. of hot water. The crystals of succinic acid melt at 182 C. To the alcoholic filtrate from the sodium succinate add 25 cc. of water and boil until the alcohol is removed. Shake the alkaline solution twice each with 10 cc. of ether and evaporate the solvent. The residue has the odor of benzyl alcohol.

Add about 1 cc. of diluted sulphuric acid to 10 cc. of tenth-normal potassium permanganate, add 0.1 Gm. of benzyl succinate and warm the mixture: the odor of benzaldehyde becomes perceptible.

The solution of benzyl succinate in alcohol (1 in 25) should be clear and colorless.

Shake 1 Gm. of finely powdered benzyl succinate with 100 cc. of water and filter: the filtrate should not be more than faintly acid to litmus paper (*succinic acid*) and separate portions should not yield precipitates with barium chloride test solution (*sulphate*), silver nitrate test solution (*chloride*) or be colored violet by ferric chloride test solution (*salicylate*).

Incinerate about 1 Gm. of benzyl succinate, accurately weighed: not more than 0.1 per cent of ash remains.

Boil about 1 Gm. of benzyl succinate, accurately weighed, for 1 hour in a reflux apparatus with 20 cc. of half normal alcoholic sodium hydroxide, cool the solution, add a few drops of phenolphthalein test solution, and titrate with half normal hydrochloric acid until the disappearance of the pink color: the amount of half-normal alcoholic sodium hydroxide consumed corresponds to not less than 99 per cent of benzyl succinate.

Benzyl Succinate-Merck.—A brand of benzyl succinate-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

Benzyl Succinate-Seydel.—A brand of benzyl succinate-N. N. R.

Manufactured by the Seydel Chemical Company, Jersey City, N. J. No U. S. patent or trademark.

BILE SALTS AND BILE SALT COMPOUNDS

The bile of man and of several animals contains the sodium salts of conjugated cholic acids in varying proportions; in ox and human biles especially glycocholic acid, $C_{26}H_{43}O_6N$; and taurocholic acid, $C_{26}H_{45}O_7NS$. Fresh ox-gall is said to contain about 3 per cent each of sodium glycocholate and sodium taurocholate.

Actions and Uses.—The bile salts constitute the main active principles of bile, and therefore share the actions and uses of the latter, perhaps with the advantage of more constant composition. When injected into the circulation, they cause severe nervous and cardiac depression, not observed when they are given by the mouth. They are generally credited with a slight antiseptic and laxative action, with enhancing the efficiency of the resinous hydragogue cathartics, and with emulsifying and hence favoring the absorption of fat. They stimulate the secretory activity of the liver, increasing both the fluids and solids of the bile.

They have been used in obstructive jaundice, although the rationale is somewhat doubtful; their use in biliary fistula is more reasonable, if the nutrition is noticeably affected.

The sodium glycocholate and taurocholate may be separated in the following manner: Dry ox-bile is treated with absolute alcohol and the tincture precipitated by ether in excess. Both salts are deposited and the glycocholate crystallizes on standing, the taurocholate remaining in amorphous form, resembling oil or resinous matter. If the deposit is dissolved in water, solution of lead acetate will throw down a lead glycocholate, while the addition of lead subacetate to the remainder will precipitate the taurocholate.

Tests: All the bile acids respond to Pettenkoffer's test. A small portion of the salt is dissolved in a little concentrated sulphuric acid in a small porcelain dish and warmed, care being taken that the temperature does not rise higher than from 60 to 70 C. A 10 per cent solution of cane sugar is then added drop by drop while the liquid is stirred with a glass rod. If compounds of cholic acid are present a beautiful red color will appear, which does not disappear at room temperature, but usually in the course of a day becomes bluish-violet. The red liquid shows in the spectrum two absorption bands, one at F and the other between D and E, nearer to E. Care must be taken not to heat too much or to add too much sugar. The sulphuric acid must be free from sulphurous acid and the lower oxides of nitrogen. As albumin, oleic acid, amyl alcohol, morphine, etc., may give a similar reaction, spectroscopic examination should not be omitted in doubtful cases (Hammarsten, Lehrbuch der physiologischen Chemie, ed. 6, p. 312). Furfurol Test (Mylius): The substance is dissolved in alcohol and for every cubic centimeter of the alcoholic solution, 1 drop of a 1 in 1000 furfurol solution and 1 cc. of concentrated sulphuric acid are added and the mixture cooled, if necessary, so that the temperature may not rise too high. The same color reaction occurs as in Pettenkoffer's test.

BILEIN.—Sodii Glyco-Taurocholas Bovis-Abbott.—A mixture of the essential salts of the bile.

Actions and Uses.—See preceding general article, Bile Salts and Bile Salt Compounds.

Manufactured by The Abbott Laboratories, Inc., North Chicago. U. S. trademark 44,140.

Bilein Pills, ¼ grain.
Bilein Pills, ⅛ grain.
Bilein Pills, 1/12 grain.

BILE SALTS-FAIRCHILD.—A preparation obtained from fresh ox-gall, consisting essentially of sodium glycocholate and sodium taurocholate, in the proportion existing in ox-bile.

Actions and Uses.—See preceding general article, Bile Salts and Bile Salt Compounds.

Dosage.—From 0.03 to 0.13 Gm. (½ to 2 grains), from 4 to 5 Gm. (60 to 75 grains), per day.

Manufactured by Fairchild Bros. and Foster, New York. No U. S. patent or trademark.

GLYCOTAURO-H. W. & D.—Bile-Salts-H. W. & D.—Concentrated ox-bile, freed from bile pigments, standardized to contain 50 per cent of the natural mixture of sodium glycocholate and sodium taurocholate. Each gram represents approximately 15 cc. of fresh ox-bile.

Actions and Uses.—See preceding general article, Bile Salts and Bile Salt Compounds.

Manufactured by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

Glycotauro-H. W. & D. Capsules, 5 grains.

Glycotauro-H. W. & D. Capsules (half size): Each contains glycotauro 0.15 Gm. (2½ grains).

Enteric Coated Glycotauro-H. W. & D. Tablets: Each contains glycotauro 2 grains (0.1 gm.) and is coated with salol.

Glycotauro is prepared by evaporating ox-bile in the presence of animal charcoal, extracting the residue with purified methyl alcohol, filtering, evaporating the filtrate and mixing the residue with glycerin.

Glycotauro is a soft semisolid mass of light brown color, bilelike odor and slightly bitter taste. It is easily soluble in water and alcohol. Its specific gravity is about 1.22.

OVOGAL.—Albumen Cholicum.—A combination of bile acids with egg albumin.

Actions and Uses. — Ovogal is said to pass the stomach without marked decomposition and to be dissolved and absorbed in the intestine.

For therapeutic indications see preceding article, Bile Salts and Bile Salt Compounds.

Dosage.—From 0.5 to 1 Gm. (8 to 15 grains), several times daily, in capsules, with water, tea, coffee or fruit juices.

Manufactured by J. D. Riedel Aktiengesellschaft, Berlin, Germany (Riedel & Co., New York). No U. S. patent. German patent 176,945. U. S. trademark 78,352.

Ovogal Capsules: Each contains ovogal 0.5 Gm. (7½ grains).

Ovogal is a greenish-yellow powder, insoluble in water, dilute acids, ether, benzol, fats, etc. Alcohol and acetone do not dissolve it, but after long action remove from it small amounts of the bile acids. Alkalis dissolve ovogal, splitting it into albumin and bile acids (glycocholic and taurocholic acid).

If 0.5 Gm. of ovogal is boiled with from 1 to 2 cc. of hydrochloric acid until a clear green solution is produced and then diluted with from 30 to 40 cc. of absolute alcohol, an abundant cloudy precipitate separates, which, when washed with alcohol until the washings are colorless, gives the characteristic reactions for proteins. On evaporation of the alcoholic filtrate, the bile acids may be recovered and identified. Ovogal on ignition should leave no weighable residue.

BISMUTH COMPOUNDS

The insoluble compounds of bismuth are used for their mechanical action as protectives of inflamed or irritated surfaces. On a wound, a fine crust is formed, beneath which healing proceeds as beneath a scab. The drying property of the powder is of the chief importance, and the antiseptic action secondary. For the best development of the protective mechanical action, a very fine division of the bismuth compound is essential. This has been secured in various ways. Soluble complex salts of bismuth, which are decomposed by dilute mineral acids with precipitation of insoluble bismuth salts in a very fine state of subdivision, are administered with the expectation that the gastric juice will bring about precipitation and thus protect the digestive tract. It is questionable whether this assumption is realized in many cases. Pharmacologists and many clinicians doubt the usefulness of all soluble bismuth preparations as a means of securing their protective action. On the other hand, the powder is given alone or prepared in a permanent suspension holding the bismuth in such a fine state of division as to favor its deposition evenly throughout the whole intestinal tract.

Bismuth has been combined with other substances, either in mixture or in synthetic compounds to produce insoluble compounds which shall be useful as a means of securing convenient administration or of enhancing protective and antiseptic actions. It is doubtful whether combination with antiseptic acids, as in bismuth subgallate or bismuth subsalicylate, increases the efficiency of the preparation. The antiseptic acids lose their power in alkaline liquids, as in the intestines; the introduction of iodine into the benzene nucleus does not increase the antiseptic power. On the other hand, bismuth compounds with phenol or with phenols in which bromine or iodine has replaced hydrogen in the benzene ring have an antiputrefactive action.

Soluble compounds of bismuth used for their protective action should be employed with caution because of the danger of absorption of poisonous amounts of bismuth. Absorption of insoluble bismuth compounds from wounds and cavities occasionally occurs. Skin lesions similar to those sometimes following the use of arsphenamine are among the most important complications of bismuth therapy. The administration of the drug should be stopped on the first sign of cutaneous irritation. Bismuth poisoning is indicated by a blue line on the gums, headache, nausea and stomatitis. Removal of the bismuth application is the principal treatment. Too free application of bismuth-containing powders or too free injection into cavities should be avoided. Large doses of bismuth subnitrate have produced nitrite poisoning by its reduction in the colon.

Most of the bismuth compounds here described belong to the insoluble type. This includes bismuth betanaphtholate, bismuth tribromphenate, cremo-bismuth and lacbismo. In bismuth oxyiodogallate the bismuth is combined with an antiseptic acid which probably adds nothing to its antiseptic power; on the other hand, bismuth betanaphtholate and bismuth tribromphenate are phenolic compounds which may reasonably be expected to have some antiseptic power.

Recently the use of bismuth has been proposed for its systemic action in the treatment of syphilis. For this purpose compounds and preparations of soluble and insoluble bismuth salts and of metallic bismuth have been employed. They are administered intramuscularly. The intravenous administration of bismuth compounds in the treatment of syphilis appears thus far to be strictly contraindicated, for the reason that the therapeutic dose of bismuth approaches too closely to the toxic when used by this route. Those who have worked with bismuth salts in treating syphilis believe that their efficiency stands between that of mercury and that of arsphenamine. The present evidence appears to show that there is warrant for the use of bismuth in the treatment of syphilis in connection with arsphenamine and mercury or as a substitute for mercury. Bismuth compounds are valuable in the treatment of syphilis in patients who are intolerant to other drugs or who show resistance to the other drugs used in syphilis by the persistence of a positive Wassermann reaction. The evidence indicates that bismuth preparations alone will not cure syphilis. Treatment with bismuth preparations is not usually injurious if the necessary precautions (observation for signs of beginning stomatitis, tests for signs of beginning nephritis) are taken.

BISMOSOL.—A sterilized solution of potassium sodium bismuthotartrate (containing 35 per cent bismuth [Bi]) 10 Gm.; piperazine, 0.3 Gm., in an aqueous solution of glucose. to make 100 cc.

Actions and Uses.—Bismosol is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see preceding article, Bismuth Compounds).

Dosage.—Bismosol is administered intramuscularly in doses of 1 cc. every two to seven days until twenty doses have been given. After an intermission of one month, a second course may be given.

Manufactured by Merck & Co., Inc., Rahway, N. J., by license of Les Etablissements Poulenc Frères, Paris. No U. S. patent. U. S. trademark 196,017.

Bismosol Ampules, 1 cc.

Bismosol is a pale yellow, syrupy liquid. On adding diluted hydrochloric acid, drop by drop, to bismosol, a gelatinous precipitate is formed which redissolves on further addition of the acid; the resulting solution yields a brownish black precipitate when saturated with hydrogen sulphide. On evaporation and ignition, bismosol yields an alkaline residue which effervesces with acids.

To 1 cc. of bismosol add three drops of acetic acid, a few drops of solution of hydrogen dioxide, one drop of ferrous sulphate solution and then an excess of sodium hydroxide solution: a purple violet color is produced. To 1 cc. bismosol add diluted hydrochloric acid drop by drop, until the precipitate which is formed has redissolved, and then add a few cubic centimeters of potassium bismuth iodide solution: a brilliant red precipitate is produced.

To 5 cc. bismosol add about 100 cc. water and sufficient hydrochloric acid to redissolve the precipitate first formed; heat the solution to from 70 to 80 C. and saturate with hydrogen sulphide to precipitate completely the bismuth as bismuth sulphide. Collect the bismuth sulphide on a tared Gooch crucible, wash successively with water, alcohol, carbon disulphide and alcohol; dry to constant weight at 110 C. The weight of bismuth sulphide is equivalent to 3.5 Gm. of bismuth (Bi) in 100 cc. of bismosol.

BISMUTH BETANAPHTHOL.—See the U. S. Pharmacopeia IX under Bismuthi Betanaphtholas.

Orphol-von Heyden.—A brand of bismuth betanaphthol.

Schering and Glatz, Inc., Bloomfield, N. J., New York, N. Y., distributor. No U. S. patent or trademark.

BISMUTH SALICYLATE.—For description see the U. S. Pharmacopeia under Bismuthi Salicylas, and the preceding article, Bismuth Compounds.

Bismuth Salicylate in Oil-P. D. & Co.: A suspension of bismuth salicylate U. S. P. in olive oil, containing 3 per cent of chlorbutanol. Each cubic centimeter contains bismuth salicylate, 0.13 Gm. (2 grains).

Prepared by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

Glaseptic Ampules Bismuth Salicylate in Oil-P. D. & Co., 1 cc.: Each ampule contains 1 cc. of a suspension of bismuth salicylate U. S. P., 0.13 Gm. (2 grains) in olive oil, containing 3 per cent of chlorbutanol.

Prepared by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

BISMUTH SODIUM TARTRATE-SEARLE. — A basic sodium bismuth tartrate containing from 72.7 to 73.9 per cent of bismuth.

Actions and Uses.—Bismuth sodium tartrate-Searle is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (See preceding article, Bismuth Compounds).

Dosage.—0.03 Gm. (½ grain) by intramuscular injection, preferably into the gluteal muscle. The initial dose is 0.015 Gm. (¼ grain), increased to 0.03 Gm. (½ grain) with the second dose and continued in two or three doses weekly for from six to ten weeks.

Manufactured by G. D. Searle & Co., Chicago. U. S. patent 1,663,201 (March 20, 1928; expires 1945). No U. S. trademark.

Ampoules Bismuth Sodium Tartrate-Searle, 2 cc.: Each ampule contains bismuth sodium tartrate-Searle, 0.03 Gm., benzyl alcohol 0.040 Gm., sucrose 0.50 Gm. in water sufficient to make 2 cc. Each ampule contains more than 2 cc. of solution.

Solution Bismuth Sodium Tartrate-Searle, 1.5 per cent: An aqueous solution containing bismuth sodium tartrate-Searle 0.015 Gm., benzyl alcohol 0.02 Gm., and sucrose 0.25 Gm., in one cubic centimeter.

Bismuth sodium tartrate-Searle is a finely divided, white powder, odorless and tasteless; permanent in air. The product is soluble in about three parts of water, except for a slight residue (0.1 per cent); the residue is soluble in sodium hydroxide solution. The aqueous solution is alkaline to litmus paper. When acid is added gradually to an aqueous solution of bismuth sodium tartrate-Searle a precipitate is produced, which dissolves on the gradual addition of an alkali.

Dissolve 0.5 Gm. of bismuth sodium tartrate-Searle in 25 cc. of water; heat to 50 C.; add 1.5 Gm. of sodium hydrosulphite dissolved in 5 cc. of 10 per cent ammonia water: a precipitate of metallic bismuth forms. To about 2 cc. of the aqueous solution (10 per cent) add a few drops of copper sulphate solution. A blue precipitate is formed, which is soluble in potassium hydroxide solution. On standing, the alkaline solution gradually deposits a precipitate. Ignite 3 Gm. in a quartz crucible, cool, and cautiously add drop by drop just sufficient nitric acid to dissolve the residue when it is warmed; pour the acid solution into 100 cc. of water, evaporate the filtrate on the water bath to 30 cc., again filter and divide the filtrate into 5 cc. portions; to one portion add an equal volume of diluted sulphuric acid: the liquid does not become cloudy (*lead*). Add an excess of ammonia water to another portion: the supernatant liquid does not exhibit a bluish tint (*copper*). Add to another portion diluted hydrochloric acid: a precipitate, insoluble in an excess of hydrochloric acid and soluble in ammonia water, is not formed (*silver*). Ignite 1 Gm. in a quartz crucible: The residue meets the requirements of Bettendorf's test, U. S. P. X, p. 430 (*arsenic*).

Dry about 1 Gm. of sodium bismuth tartrate-Searle, weighed accurately, at 100 C. to constant weight: the loss is from 2.6 to 3.6 per cent. Dissolve about 0.5 Gm. of bismuth sodium tartrate-Searle, accurately weighed, in 20 to 30 cc. of water and add sufficient hydrochloric acid to redissolve the precipitate first formed; saturate the solution with hydrogen sulphide; collect the precipitate of bismuth sulphide, wash it successively with water, alcohol, carbon disulphide, and ether and dry it at 100 C.: the weight of bismuth sulphide is equivalent to not less than 72.7 nor more than 73.9 per cent of bismuth (Bi).

BISMUTH TRIBROMPHENATE.—**Bismuthi Tribromphenas.**—Bismuth Tribromphenol.—Xeroform.—A basic bismuth tribromphenate of variable composition.

Actions and Uses.—Bismuth tribromphenate is claimed to be a nonirritant and nontoxic antiseptic. It is said to be useful as an odorless and efficient substitute for iodoform; as valuable in ulcus cruris and all weeping eczemas; internally, in gastro-intestinal catarrh, proctitis, dysentery, bacillary and choleraic diarrhea, cholera infantum, etc.

Dosage.—From 1 to 3 Gm. (15 to 45 grains) per day to adults; from 0.125 to 0.3 Gm. (2 to 5 grains) at a dose to children. Externally (as a dusting powder, in bandages, etc.) like iodoform.

An amorphous, yellow, nearly odorless and tasteless powder, neutral to moistened litmus paper. It is only slightly soluble in water, alcohol, chloroform, liquid petrolatum and vegetable oils. Alkalis and strong acids decompose it. It is stable at temperatures below 120 C.

Boil about 1 Gm. of the salt with 10 cc. of sodium hydroxide solution, filter the liquid and acidulate the filtrate with sulphuric acid: the white curdy precipitate produced, when washed and dried, melts at from 90 to 95 C. (*tribromphenol*). The contents of the filter dissolve completely in diluted hydrochloric acid (*insoluble inert material*)

Boil 1 Gm. of bismuth tribromphenate with 20 cc. of a mixture of equal parts of acetic acid and water, cool the solution and filter. Free the filtrate from bismuth by saturating with hydrogen sulphide, boil the mixture and again filter: the latter filtrate leaves not more than 0.005 Gm. of residue on evaporation and gentle ignition (*alkalis and alkali earths*).

Shake 2 Gm. of bismuth tribromphenate, 20 cc. of ether, and 20 cc. of a mixture of equal volumes of hydrochloric acid and distilled water in a separatory funnel for one or two minutes. Draw off the aqueous portion and concentrate to about 4 cc.; pour it into 100 cc. of distilled water, filter, evaporate the filtrate on the water bath to 30 cc., again filter and divide this filtrate into portions of 5 cc. each. Mix one portion with an equal volume of diluted sulphuric acid: it does not become cloudy (*lead*). Treat another portion with a slight excess of ammonia water: the supernatant liquid does not exhibit a bluish tint (*copper*); another portion is not immediately affected by barium nitrate test solution (*sulphate*).

Heat gently a mixture of about 0.2 Gm. of bismuth tribromphenate with 5 cc. of potassium hydroxide solution and about 0.2 Gm. of aluminum wire; the vapors evolved do not turn red litmus blue (*nitrates*).

Shake 1 Gm. of bismuth tribromphenate frequently during fifteen minutes with 30 cc. of alcohol (95 per cent), filter and rinse flask with two separate 10 cc. portions of alcohol, allowing the washings to run through filter. To the combined filtrate and washings add 5 cc. of tenth-normal sodium hydroxide, using a few drops of phenolphthalein solution as an indicator and determine the excess of alkali with tenth-normal hydrochloric acid: not more than 1 cc. of tenth-normal sodium hydroxide should have been consumed by the alcoholic liquid (*free tribromphenol*).

Add 2 cc. of nitric acid to 2 Gm. of bismuth tribromphenate in a porcelain crucible, carefully evaporate to dryness on a sand bath and incinerate. Dissolve the residue in 5 cc. of concentrated hydrochloric acid and add to the solution 10 cc. of a saturated solution of stannous chloride in concentrated hydrochloric acid: the mixture should not darken on standing thirty minutes (*arsenic*).

Mix 0.5 Gm. of the salt with 10 cc. of a mixture of equal parts of hydrochloric acid and distilled water: no effervescence should occur (*carbonate*).

To about 0.5 Gm. of bismuth tribromphenate, accurately weighed, add 20 cc. of hydrochloric acid and digest on water bath. Add 150 cc. of water and filter. Rinse the beaker with 30 cc. of acidulated water and allow the washings to run through the filter. Saturate the combined filtrate and washings with hydrogen sulphide (care being exercised that the solution is not too acid so as to prevent quantitative precipitation of the bismuth sulphide), filter off the bismuth sulphide, wash and dissolve in hot dilute nitric acid. Add a slight excess of ammonia water followed by 2 cc. of ammonium carbonate test solution. Allow to stand thirty minutes, filter off the precipitated bismuth hydroxide and heat to constant weight at dull red heat: the residue of bismuth oxide (Bi_2O_3) should be not less than 45 per cent nor more than 55 per cent of the original weight of bismuth tribromphenate taken, corresponding to not less than 40 per cent nor more than 49 per cent of bismuth.

Xeroform-S. and G.—A brand of bismuth tribromphenate-N. N. R.

Marketed by Schering and Glatz, Inc., Bloomfield, N. J., and New York, N. Y. No U. S. patent or trademark.

CREMO-BISMUTH. — Milk of Bismuth-Mulford. — A mixture consisting of bismuth subcarbonate, suspended in water in a finely divided state, each hundred cubic centimeters representing the equivalent of 8.66 Gm. (40 grains in 1 fluidounce) of bismuth subnitrate.

Dosage.—From 4 to 15 cc. (1 to 4 fluidrachms), every two or three hours.

Prepared by the H. K. Mulford Company, Philadelphia. U. S. trademark 29,335.

LAC BISMO.—Mistura Bismuthi-Hart.—A mixture said to consist of bismuth hydroxide and bismuth subcarbonate, suspended in water, in a finely divided state, and containing 0.15 Gm. (2½ grains) of the salts in 4 cc. (1 fluidrachm).

Dosage.—From 4 to 15 cc. (1 to 4 fluidrachms).

Prepared by E. J. Hart & Company, Ltd., New Orleans. U. S. trademark.

MESUROL.—Benzobis.—Basic Bismuth Methoxy Hydroxy Benzoate.—A basic bismuth salt of methoxyhydroxybenzoic acid, of variable composition, containing from 54 to 57 per cent of bismuth.

Actions and Uses.—Mesurol is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis.

Dosage.—Mesurol is administered intramuscularly in the form of emulsion mesurol, 20 per cent. The initial dose is 0.5 cc., increased to 1 cc. at the second dose and continued until from eight to twelve doses have been administered.

Manufactured by the Bayer Company, Rensselaer, N. Y. (Winthrop Chemical Company, Inc., New York, distributor). U. S. patent 1,522,054 (Jan. 6, 1925; expires 1942). U. S. trademark 226,373.

Emulsion Mesurol, 20 per cent: A suspension of mesurol in sesame oil, each cubic centimeter of which contains mesurol equivalent to from 0.103 to 0.117 Gm. of bismuth (Bi).

Mesurol is a yellowish gray powder, insoluble in water and in most organic solvents.

Suspend about 0.05 Gm. of mesurol in 5 cc. of water, add 5 cc. of ammonium sulphide: the solid blackens. Suspend 0.1 Gm. in 5 cc. of water, acidify with hydrochloric acid and allow to cool: crystals appear, which, on addition of ferric chloride solution, causes the formation of a deep blue color; the crystals, after drying, melt at 152 C.

Agitate 1 Gm. of mesurol with 20 cc. of chloroform, filter the liquid and evaporate the filtrate to dryness: not more than 0.005 Gm. of residue remains (*freemethoxyhydroxybenzoic acid*). Ignite 3 Gm. in a quartz crucible, cool, and cautiously add drop by drop just sufficient nitric acid to dissolve the residue when it is warmed; pour the acid solution into 100 cc. of distilled water, evaporate the filtrate on the water bath to 30 cc., again filter and divide the filtrate into 5 cc. portions; to one portion add an equal volume of diluted sulphuric acid: the liquid does not become cloudy (*lead*). Add an excess of ammonia water to another portion: the supernatant liquid does not exhibit a bluish tint (*copper*). Add to another portion diluted hydrochloric acid: a precipitate, insoluble in an excess of hydrochloric acid and soluble in ammonia water, is not formed (*silver*). Boil 1 Gm. in 70 cc. of water, add hydrochloric acid in small portions to the boiling suspension until the suspended particles dissolve, saturate with hydrogen sulphide and filter; evaporate the filtrate to a small bulk, cool, transfer to a platinum dish, add 2 cc. of sulphuric acid, evaporate to dryness and ignite: the residue weighs less than 0.005 Gm. (*alkali or alkaline earth salts*). Triturate about 0.05 Gm. with 0.1 Gm. of sodium salicylate and 5 cc. of distilled water, superimpose the mixture on 5 cc. of sulphuric acid: no pink or brownish red zone is observed at the line of contact (*nitrate*). Suspend 0.06 Gm. in boiling water, add diluted nitric acid in small portions until the suspended particles dissolve, cool, dilute to 50 cc., add 1 cc. of silver nitrate solution: a precipitate is not formed (*chloride*).

Transfer about 2 Gm. of mesurol, accurately weighed, to a quartz crucible; dry to constant weight at 100 C.: the loss in weight at 100 C. is not more than 1 per cent. Ignite the dried product and after cooling add 5 cc. of nitric acid drop by drop to the residue, warming until solution has been effected, evaporate to dryness, carefully ignite it at red heat, and weigh the resulting bismuth oxide: the residue corresponds to not less than 54 per cent nor more than 57 per cent of bismuth. The residue meets the requirements of Bettendorf's test, U. S. P. X, page 430 (*arsenic*).

OLEO-BI-ROCHE.—A suspension of finely divided bismuth oleate, $Bi(C_{17}H_{33}COO)_3$, in olive oil, containing bismuth oleate equivalent to 0.05 Gm. of bismuth (Bi) in each cubic centimeter.

Actions and Uses.—Oleo-Bi-Roche is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see preceding article, Bismuth Compounds).

Dosage.—Two cc. intramuscularly, preferably into the gluteal muscle, two or three times a week; in the case of adults, from twelve to twenty injections of 2 cc. are proposed as a course of treatment.

Manufactured by F. Hoffmann-LaRoche and Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J., distributor). U. S. patent 1,547,165 (July 28, 1925; expires 1942). U. S. trademark 183,191.

Ampules Oleo-Bi-Roche, 2 Cc.

In the manufacture of Oleo-Bi-Roche, moist bismuth oleate is emulsified and dehydration takes place subsequently. The bismuth oleate used complies with the following standards:

It is a soft, amorphous mass, insoluble in water; partially soluble in alcohol and ether. Its bismuth content is 19.8 per cent. and its oleic acid content about 77.8 per cent.

Suspend about 1 Gm. of bismuth oleate in 10 cc. of ether. Shake the mixture with 10 cc. of diluted hydrochloric acid, draw off the aqueous layer and cautiously pour diphenylamine solution over it: a blue zone does not appear (*nitrate*).

Introduce about 1.5 Gm. of moist bismuth oleate (representing 0.1 to 0.3 Gm. of Bi), accurately weighed, into a beaker of 50 cc. capacity. Pour 20 cc. of ether over the bismuth oleate and stir with a glass rod. Transfer the turbid liquid to a separator and complete the transfer with three portions of ether of 5 cc. each. Add 5 cc. of nitric acid (25 per cent) to the contents of the separator and agitate the contents for one to two minutes. When separation has occurred, draw the aqueous portion into a beaker. Extract the etheral liquid in the separator three times with 5 cc. portions of liquid diluted nitric acid and add the washings to the contents of the beaker. Dilute the acid extractions with water to make about 80 cc. Add a drop of methyl orange solution to the liquid and neutralize it with 10 per cent ammonnum carbonate solution (cover the beaker with a watch glass to avoid loss by spattering) and then add a further quantity of 5 cc. of 10 per cent ammonium carbonate solution. Complete the determination in the usual way and weigh as bismuth oxide.

Introduce about 1.5 Gm. of moist bismuth oleate into a 50 cc. beaker and weigh accurately. Add 20 cc. of ether and stir with a glass rod. Transfer the mixture to a 50 cc. separator and complete the transfer with three 5 cc. portions of ether. Add 5 cc. of 25 per cent nitric acid to the liquid in the separator and agitate the mixture. After separation, draw off the acid liquid and then extract the ether solution with three 5 cc. portions of 10 per cent nitric acid and finally with 5 cc. portions of water until the washings are neutral to litmus. Filter the ether solution into a small flask and complete the transfer with ether. Remove the ether in the flask by distillation, dissolve the residue in 30 cc. of neutral alcohol and determine the acidity of the solution by titration with tenth-normal sodium hydroxide, using phenolphthalein as indicator. From the volume of tenth normal alkali consumed, calculate the percentage of oleic acid.

POTASSIUM BISMUTH TARTRATE-D. R. L.—A basic potassium bismuth tartrate containing from 64 to 69 per cent of bismuth.

Actions and Uses.—Potassium Bismuth Tartrate-D. R. L. is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see preceding article, Bismuth Compounds).

Dosage.—From 0.1 to 0.2 Gm. (1½ to 3 grains) by intramuscular injection, preferably into the gluteal muscle. The injections may be repeated at intervals of from four to seven days until a total of from 2.4 to 3.0 Gm. has been given.

Manufactured by The Abbott Laboratories, North Chicago. No U. S. patent or trademark.

Ampules Potassium Bismuth Tartrate with Butyn-D. R. L., 0.1 Gm.: Each ampule contains potassium bismuth tartrate-D. R. L. 0.1 Gm. and butyn, 0.012 Gm. suspended in 2 cc. of expressed oil of almonds.

Ampules Potassium Bismuth Tartrate with Butyn-D. R. L., 0.2 Gm.: Each ampule contains potassium bismuth tartrate-D. R. L. 0.2 Gm. and butyn, 0.012 Gm. suspended in 2 cc. of expressed oil of almonds.

Potassium Bismuth Tartrate with Butyn-D. R. L., 10 per cent: Each cc. contains potassium bismuth tartrate-D. R. L., 0.1 Gm.; butyn, 0.6 per cent; and metaphen, 0.01 per cent suspended in expressed oil of almonds.

Potassium bismuth tartrate-D. R. L. is a finely granular, white powder; odorless, and having a sweetish taste; permanent in the air. It is soluble in water; insoluble in alcohol, ether or chloroform; soluble with decomposition in dilute mineral acids; almost completely soluble in solutions of the alkalies. Its solutions are decomposed by solutions of most alkaloids and local anesthetics. At 100 C. the salt loses a part of its water of hydration and on further heating, at a higher temperature, it carbonizes and leaves a residue which contains potassium carbonate, metallic bismuth and bismuth oxide.

To about 2 cc. of the aqueous solution (10 per cent) add a few drops of copper sulphate solution. A blue precipitate is formed, which is soluble in potassium hydroxide solution. On standing, the alkaline solution gradually deposits a precipitate. To about 5 cc. of the aqueous solution (10 per cent) add a small crystal of potassium dichromate: a yellow precipitate forms which is not soluble in potassium hydroxide solution. To about 5 cc. of the aqueous solution (10 per cent) add a few drops of silver nitrate solution: a white precipitate results. On boiling the mixture blackens and a mirror forms. The aqueous solution (10 per cent) gives a white precipitate with barium chloride solution and a black precipitate of metallic bismuth with sodium hydrosulphite solution.

Boil about 1 Gm. of potassium bismuth tartrate-D. R. L., accurately weighed, with 20 cc. of alcohol for 15 minutes, filter, evaporate the filtrate in a weighed dish, cool and weigh the residue, if any: the soluble matter should not amount to more than 0.5 per cent. To about 0.2 Gm. of potassium bismuth tartrate-D. R. L., accurately weighed, and 2 Gm. of potassium permanganate, add 5 cc. of 10 per cent sulphuric acid, allow the mixture to react for 15 minutes and then thoroughly mix with 15 cc. of concentrated sulphuric acid. Decolorize the resulting mixture with hydrogen perioxide solution, dilute it with 35 cc. of water, boil the solution for 5 minutes and finally dilute it with 150 cc. of water. Saturate the liquid with hydrogen sulphide, collect the precipitate in a weighed Gooch crucible, wash it successively with hydrogen sulphide water, distilled water, methyl alcohol, carbon disulphide, methyl alcohol (again) and ether, dry at 110 C. and weigh: the weight of bismuth sulphide obtained corresponds to from 64 to 69 per cent of bismuth.

BROMINE DERIVATIVES

Synthetic compounds containing bromine have been produced with the purpose of securing the sedative action of bromine without the objectionable effects of the alkali bromides. These compounds split off bromine ions in the system, the decomposition being due to the oxidation of the organic substance with which it is combined; but bromine which is too firmly bound may fail to exert its typical effects. As the usual indications for bromine action in the organism require a prompt and powerful action on the cells to produce sleep, to abolish reflexes or to arrest an epileptic paroxysm, the synthetic compounds are apt to fail as substitutes for the alkali bromides because their bromine is too slowly evolved. The introduction of bromine into compounds already possessing hypnotic or sedative powers may result in increasing the efficiency of these compounds.

BROMETONE. — Tribromtertiarybutylalcohol. — Acetonebromoform. — $CBr_3.C(OH)(CH_3).CH_3$. — 1,1,1-tribrom-2-methylpropan-2-ol produced by the reaction of acetone on bromoform.

Actions and Uses.—Brometone is claimed to have the sedative action of the bromides without the disadvantage of producing bromism. In doses of 0.3 Gm. (5 grains), four or five times a day, in adults, it is claimed that brometone causes no unpleasant results, produces no disturbance of the digestive organs, and has no appreciable effect on the secretions. Its action is prompt and its effect is manifest for several hours. In doses exceeding 1.6 Gm. (25 grains), daily, it may produce dizziness, vertigo, anorexia and mental hebetude, all of which symptoms disappear on discontinuance of its use. Therapeutically, this drug has been said to be useful in mild conditions of excitation and insomnia, in so-called narcotic abstinence, in hysteria, and in nervous affections generally. It relieves some forms of cough and it is said to produce amelioration in some cases of epilepsy. It has been used to relieve dizziness due to labyrinthine disturbances.

Dosage.—The dose is 0.3 Gm. (5 grains), dry or in capsules, to be repeated two or three times during twenty-four hours.

Manufactured by Parke, Davis & Company, Detroit. U. S. trademark.

Brometone Capsules, 5 grains.

Brometone occurs in fine white, prismatic crystals which possess a camphoraceous odor and taste. It is slightly soluble in water, soluble in alcohol, ether, benzin and most organic solvents. It melts at about 167 C. and volatilizes on exposure to air.

BROMIPIN 10 PER CENT.—Brominized Sesame Oil, 10 per cent-Merck. A bromine addition product of sesame oil, containing from 9.8 to 11.2 per cent of bromine in organic combination.

Actions and Uses.—Bromipin, 10 per cent, acts like the inorganic bromides. The combination is not broken up in the stomach; but a portion of the bromine is split off as soon as the compound enters the intestine; the remaining compound is readily absorbed, and, as in the case of other fats, it is largely deposited in the tissues where it is slowly split up. Bromipin, 10 per cent, is said to be more lasting in its action than the bromides.

Dosage.—Four cc. (1 fluidrachm), which may be increased in cases of epilepsy to from 8 to 30 cc. (2 to 8 fluidrachms). It may be given in emulsion with peppermint water and syrup, or pure, flavored with oil of peppermint.

Marketed by Merck & Co., Inc., Rahway, N. J., under U. S. patent 774,224 (issued Nov. 8, 1904; expired), by license of Chemical Foundation, Inc., U. S. trademark 32,002.

Bromipin 10 per cent is prepared by action of bromine chloride to produce the required brominization.

Bromipin 10 per cent is a yellow oily liquid, having an oleaginous taste.

To 1 cc. of bromipin 10 per cent add 1 cc. of chloroform and a few drops of phenolphthalein solution: the addition of 0.3 cc. of half-normal sodium hydroxide produces a red color (*limit of acidity*).

Saponify about 3 Gm. of bromipin 10 per cent, accurately weighed, by boiling with 25 cc. of alcohol and 5 Gm. of potassium hydroxide in a porcelain dish. Evaporate to dryness on a water bath and incinerate the residue over a gentle flame. Dissolve in water to make exactly 200 cc. and filter. Acidulate 50 cc. of the filtrate in a separator with diluted sulphuric acid; add 20 cc. of carbon tetrachloride and 5 cc. of freshly prepared chlorine water. Shake thoroughly and allow to separate. Repeat this until further additions of chlorine water do not cause the aqueous layer to become yellow. Draw off the carbon tetrachloride solution. Add 10 cc. of carbon tetrachloride, agitate and draw off the solution, uniting it with the first carbon tetrachloride solution. Repeat the extraction with a further portion of 5 cc. of carbon tetrachloride. Pass the carbon tetrachloride solution through a dry filter into a flask and add potassium iodide solution. Shake thoroughly and titrate the free iodine with tenth-normal sodium thiosulphate: the amount of bromine found is not less than 9.8 per cent, nor more than 11.2 per cent.

BROMIPIN 33 PER CENT.—Brominized Sesame Oil, 33 Per Cent-Merck.—A bromine addition product of sesame oil, containing from 31 to 35 per cent of bromine in organic combination.

Actions and Uses.—Bromipin, 33 per cent, acts like the inorganic bromides. The combination is not broken up in the stomach; but a portion of the bromine is split off as soon as the compound enters the intestine; the remaining compound is readily absorbed and, as in the case of other fats, is largely deposited in the tissues where it is slowly split up. It is said to be more lasting in its action than the bromides. Bromipin, 33 per cent, is used as a contrast medium for roentgen diagnosis of the tracheobronchial tree. It is stated to be applicable in cases of mild or medium tuberculosis in which the use of an iodized oil is contraindicated.

Dosage.—For therapeutic use, 1.3 cc. (20 minims) which may be increased in cases of epilepsy to from 3 to 10 cc. (40 to 160 minims); for use as a contrast medium in bronchography, the quantity required varies from about 10 cc. to about 30 cc. for each lung. Before injecting into the bronchial tree the oil should be warmed to 37 to 40 C. to reduce its viscosity.

Marketed by Merck & Co., Inc., Rahway, N. J., under license of the Federal Trade Commission. U. S. patent 774,224 (Nov. 8, 1904; expired). U. S. trademark 32,002.

Bromipin, 33 per cent, is prepared by action of bromine chloride to produce the required brominization.

Bromipin 33 per cent is a yellow oily liquid, having an oleaginous taste.

To 1 cc. of bromipin 33 per cent add 1 cc. of chloroform and a few drops of phenolphthalein solution: the addition of 0.3 cc. of half-normal sodium hydroxide produces a red color (*limit of acidity*).

Saponify about 1 Gm. of bromipin 33 per cent, accurately weighed, by boiling with 25 cc. of alcohol and 5 Gm. of potassium hydroxide in a porcelain dish. Evaporate to dryness on a water bath and incinerate the residue over a gentle flame. Dissolve in water to make exactly 200 cc. and filter. Acidulate 50 cc. of the filtrate in a separator with diluted sulphuric acid; add 20 cc. of carbon tetrachloride and 5 cc. of freshly prepared chlorine water. Shake thoroughly and allow to separate. Repeat this until further additions of chlorine water do not cause the aqueous layer to become yellow. Draw off the carbon tetrachloride solution. Add 10 cc. of carbon tetrachloride, agitate and draw off the solution, uniting it with the first carbon tetrachloride solution. Repeat the extraction with a further portion of 5 cc. of carbon tetrachloride. Pass the carbon tetrachloride solution through a dry filter into a flask and add potassium iodide solution. Shake thoroughly and titrate the free iodine with tenth-normal sodium thiosulphate: the amount of bromine found is not less than 31 per cent nor more than 35 per cent.

BROMURAL.—$(CH_3.CH(CH_3)CHBr.CO)HN.CO.NH_2$.—2-monobromisovalerylurea, obtained by the interaction of urea with bromisovaleryl bromide.

Actions and Uses.—Bromural is a nerve sedative which produces sleep in mild cases of insomnia without markedly affecting the circulation or respiration. All action by bromural is said to cease after from three to five hours. In many cases, however, the sleep caused by the preparation continues beyond the limits of its action. It is claimed to be useful as a nerve sedative and for the purpose of inducing sleep in functional nervous disease. Bromural is not effective in cases of insomnia associated with pain, cough, angina pectoris or delirium.

Dosage.—As a nerve sedative, 0.3 Gm. (5 grains), three times daily; as a hypnotic at bedtime, 0.6 Gm. (10 grains), which dose may be repeated if advisable during the night, after the action of the first dose has ceased.

Manufactured by E. Bilhuber, Inc., New York, by license of the Chemical Foundation, Inc. U. S. patent 914,518 (March 9, 1909; expired). U. S. trademark 61,165.

Bromural Tablets, 5 grains (0.3 Gm.).

Bromural forms small, white, almost tasteless needles which are easily soluble in hot water, ether, alcohol and alkalis, but less readily in cold water. It sublimes on heating and melts at from 147 to 149 C.

Bromural can be precipitated from a 10 per cent sodium hydroxide solution with acids. The presence of bromine may be demonstrated by fusion with sodium carbonate and potassium nitrate and testing for a bromide with silver nitrate solution. On heating the alcoholic solution of bromural with sodium ethylate for several hours on the water bath, sodium bromide will precipitate. If this is filtered off and the filtrate evaporated, a crystalline mass remains which can be recrystallized from water. This is dimethylacrylic acid, melting at 280 C. If 1 Gm. of bromural is boiled for about one minute with 10 per cent solution of sodium hydroxide, ammonia obtained from the urea will be given off. If the hot liquid is then cooled, acidified with nitric acid and extracted with ether, and the ether evaporated, an oily fluid, 1-brom-isovaleric acid, which has the specific odor of valeric acid, will remain. The biuret reaction cannot be obtained. On melting bromural and adding concentrated sodium hydroxide solution and copper sulphate, no color reaction will take place.

CARBROMAL.—For description see the U. S. Pharmacopeia under Carbromalum.

Actions and Uses.—Carbromal is said to be an efficient and prompt sedative, reducing excitement and promoting sleep in conditions in which a powerful hypnotic is not required. In therapeutic doses it is said not to exert any unfavorable influence on the respiration or heart action. The sleep produced is said to be restful, dreamless and exceptionally free from unpleasant by-effects and sequelae.

Carbromal is stated to be useful as a sedative and mild hypnotic in neurasthenia, hysteria, cardiac neuroses with tachycardia, chorea, mental disorders with moderate excitement, insomnia due to various internal diseases, etc.

Dosage.—As a sedative from 0.3 to 0.6 Gm. (5 to 10 grains), given in cold water, repeated three or four times daily if necessary; as a hypnotic from 0.6 to 1.3 Gm. (10 to 20 grains), followed by a drink of hot, sweetened water or weak tea.

Adalin.—A brand of carbromal-U. S. P.

Manufactured by Bayer Company, Rensselaer, N. Y. (Winthrop Chemical Company, Inc., New York, distributor). U. S. patent 983,425 (Feb. 7, 1911; expires 1928). U. S. trademark 81,136.

Adalin Tablets, 5 grains (0.3 Gm.).

SABROMIN. — Calbroben. — Calcium Dibrombehenate $Ca(C_{21}H_{41}Br_2.COO)_2$. Sabromin contains not less than 28.5 per cent of bromine.

Actions and Uses.—Sabromin is converted in the stomach into dibrombehenic acid, and this is absorbed from the intestinal tract. The absorption and elimination are slower than that of the inorganic bromides; hence, sabromin is not adapted to conditions in which a rapid saturation of the system with bromine is required. It is indicated in conditions in which the bromides cannot be administered for continued periods without gastric disturbance or in which brominism is caused readily. It is claimed that sabromin is of value in conditions in which a mild sedative action is desired, particularly in conditions requiring prolonged administration, and that because of absence of taste, it is of value in pediatric practice.

Dosage.—For adults, from 0.3 to 1.2 Gm. (5 to 20 grains). When administered in the form of tablets, these should be masticated before swallowing.

Manufactured by the Bayer Company, Inc., Rensselaer, N. Y. (Winthrop Chemical Company, Inc., New York, distributor). U. S. patent 848,230 (March 26, 1907; expired). U. S. trademark 74,091.

Sabromin Tablets, 8 Grains.

Sabromin is a yellowish white powder; odorless and tasteless. It is insoluble in water and alcohol, but soluble in ether, chloroform, acetone, benzene, petroleum benzin and carbon tetrachloride.

Shake about 0.5 Gm. of sabromin with 10 cc. of boiling water and filter. The filtrate is neutral to litmus paper and gives not more than a slight opalescence with silver nitrate solution (*soluble bromides*), and no precipitate with barium chloride solution (*sulphates*).

Heat about 0.2 Gm. of sabromin with 5 cc. of sodium hydroxide solution for one minute. Dilute the solution with 5 cc. of water, acidulate with acetic acid, filter, and divide the filtrate into two portions. To one portion add ammonium oxalate solution. A white precipitate results (*calcium*); shake the second portion with 5 cc. of dilute hydrochloric acid; add 10 drops of chlorine water and 5 cc. of chloroform and agitate the mixture: after separation, the chloroform shows a yellow coloration (*bromine*).

Dry about 1 Gm. of sabromin, accurately weighed to constant weight at 100 C.: the loss is not more than 2.5 per cent (*limit of moisture*).

Dissolve 0.25 Gm. of sabromin in 5 cc. of chloroform and add 3 drops of absolute alcohol: not more than a slight opalescence is produced, and only a very slight precipitate occurs after standing for twenty-four hours.

Boil about 2 Gm. of sabromin, accurately weighed, in a reflux apparatus with 100 cc. of 10 per cent alcoholic potassium hydroxide for six hours. Transfer the solution to a porcelain evaporating dish and evaporate the alcohol over a water bath. Dilute the residue with a little water, pour the solution into a 500 cc. flask, and add 40 cc. of 30 per cent nitric acid. Dilute to 500 cc. with water, shake well and filter. To 250 cc. of the filtrate add 20 cc. of nitric acid and 50 cc. of tenth-normal silver nitrate. Titrate the excess of silver salt with tenth-normal potassium sulphocyanate solution, using ferric ammonium sulphate as indicator: the tenth-normal silver nitrate consumed corresponds to not less than 28.5 per cent of bromine.

Heat about 2 Gm. of dried sabromin, accurately weighed, until most of the carbon has been consumed; extract the residue with hot, diluted hydrochloric acid; filter; add a slight excess, each of ammonia water and ammonium oxalate solution; collect the precipitate, dry it and ignite it to calcium oxide in the usual way: the weight of calcium oxide corresponds to not less than 3.5 per cent of calcium.

CALCIUM COMPOUNDS

Calcium performs important functions, especially in forming the structure of bone, the regulation of nervous, muscular and glandular activity and in the coagulation of the blood. In rickets, osteomalacia and osteopsathyrosis there is defective deposition of calcium in the bones, but this is usually due to factors other than a deficient supply of calcium; and these conditions are not benefited by the administration of calcium salts except in rare experimental conditions, when calcium has been almost totally lacking in the diet. When the calcium content of the blood is low, as in infantile and parathyroid tetany, the administration of calcium salts results in a temporary increase in blood calcium and a cessation of the symptoms, but unless the cause of the condition is removed, the concentration sinks rapidly following discontinuance of calcium administration. Administration of the parathyroid hormone leads to an increase in blood calcium even though additional calcium is not supplied.

The administration of calcium salts has been shown to lessen certain transudation phenomena. For this reason it has been found useful against the skin rashes of serum disease, urticaria and angioneurotic edema and certain forms of diarrhea. It is unreliable against ascites and other generalized edemas. It has been reported as being effective in preventing arsphenamin reactions and also in certain dermatoses as dermatitis herpetiformis, lichen rubra and erythema pernio, but further observations are needed in these directions. A deficiency of calcium in the circulating fluids leads to increased excitability of the neuromuscular system, as is seen for example in tetany. The administration of calcium salts decreases the neuromuscular irritability in such cases. The intravenous infusion of soluble calcium salts causes a constriction of the blood vessels and a marked contraction of the pupils.

Calcium is necessary for blood coagulation, but a large excess lengthens the coagulation time. The effect of calcium on blood coagulation has led to its injudicious use in hemorrhagic conditions, such as hemophilia, purpura and the intestinal hemorrhage of typhoid fever. It is very improbable that it is effective in any of these conditions, as in all of them the blood contains an adequate amount of calcium. It has been claimed that the administration of calcium salts to jaundiced patients is effective in preventing postoperative hemorrhage. There is, however, very little evidence that this is the result of shortening of the coagulation time. It has been shown that the administration of calcium salts tends to diminish the toxicity of carbon tetrachloride. When calcium chloride is administered, the basic portion of the molecule is, to a large extent, excreted by way of the bowel. The acid portion is metabolized in the same manner as hydrochloric acid, decreasing the alkali reserve of the body and increasing the acidity of the urine. Large doses of calcium chloride may produce acidosis. Calcium chloride is one of the substances which may be administered to render the urine acid during treatment with methenamin.

Intravenously, overdoses of any calcium compound may be fatal by paralyzing the heart and central nervous system.

The average normal diet usually contains just about enough calcium for the needs of the body, but when unusual diets are taken there may be a calcium deficiency. This may be remedied by the administration of natural foods having a high calcium content, such as milk, green vegetables and egg yolk. The administration of special preparations of calcium salts is indicated only in special pathological conditions, especially tetany. The administration of calcium salts in the treatment of rickets or other diseases associated with deficient calcification is in itself inefficient, but may be used as an adjunct in the treatment when vitamin D is also administered. On oral administration, calcium chloride is at times more effective in raising blood calcium than are the organic salts of calcium. This effect may be in part explained by the acidosis caused by calcium chloride administration. The lactate and gluconate are, however, more pleasant to take than calcium chloride and are less irritating. Calcium chloride cannot be used for subcutaneous or intramuscular injection as it is too irritating. It may, however, be used intravenously. For hypodermic or intramuscular use, the less irritant lactate or the non-irritant gluconate are employed.

AFENIL.— Calcium chloride urea.— $CaCl_2.4(NH_2)_2CO$.— Afenil is a molecular compound of calcium chloride and urea.

Actions and Uses.—Afenil has the actions of calcium chloride. It is claimed that afenil solutions when administered intravenously, are better tolerated and less irritating than solutions of calcium chloride.

Dosage.—Afenil is marketed in ampules containing 10 cc. of a 10 per cent solution of afenil. Each injection consists of the entire contents of one ampule.

Manufactured by Knoll and Co., Ludwigshafen a. R., Germany (E. Bilhuber, Inc., New York). No U. S. patent. U. S. trademark 170,032. German patent 306,804.

Ampules Afenil: Each ampule contains 10 cc. of a sterile 10 per cent solution of afenil (equivalent to 0.11 Gm. Ca).

Afenil occurs as colorless crystals; non-hydroscopic; very soluble in water.

The calcium content of afenil is determined by precipitating with ammonium oxalate in the usual way and weighing as calcium oxide. The urea content of afenil is determined by an estimation of nitrogen by the Kjeldahl method.

CALCIUM GLUCONATE-SANDOZ.—Normal Calcium Gluconate.—Calcium salt of hexapentol-(2,3,4,5,6)-Acid-(1).—Calcium salt of $\alpha\beta\gamma\delta\epsilon$ pentoxy-pentane-carbonic acid.—$[HOCH_2-CH(OH)CH(OH)CH(OH)CH(OH)COO]_2Ca \cdot H_2O$. It contains calcium equivalent to not less than 12.40 nor more than 12.80 per cent of calcium oxide.

Actions and Uses.—Calcium gluconate-Sandoz is used to obtain the therapeutic effects of calcium. It is more palatable than calcium chloride for oral administration and for hypodermic or intramuscular use is nonirritant.

Dosage.—Orally, for adults, 5 Gm. (75 grains) three times a day; for children, 2 Gm. (30 grains) three times a day. Intramuscularly or intravenously, for adults, 1 Gm. administered every day, on alternate days or every third day; for children, 0.2 to 0.5 Gm. administered every day, on alternate days or every third day.

Manufactured by the Sandoz Chemical Works, Basle, Switzerland (Sandoz Chemical Works, Inc., New York, distributor). U. S. patent 1,648,368.

Ampules Calcium Gluconate-Sandoz: Each ampule contains 10 cc. of a 10 per cent stabilized supersaturated solution of calcium gluconate-Sandoz.

Calcium gluconate-Sandoz occurs as white, odorless and tasteless granules, consisting of fine needle crystals. It crystallizes from an aqueous solution with one molecule of water and has the formula $(C_6H_{11}O_7)_2Ca.H_2O$. It loses completely its water of crystallization only after prolonged drying in a high vacuum at 105 C. A 3 per cent aqueous solution is slightly dextrorotatory. When heated it swells up, and during carbonization emits an odor of burning filter paper. It is soluble in cold water (1 in 30); soluble in boiling water (1 in 4 to 5), crystallizing on cooling. It possesses distinct tendencies to form supersaturated solutions. It is insoluble in alcohol and fat solvents. Cold, saturated aqueous solutions are neutral to litmus paper. Addition of diluted sulphuric acid to a 3 per cent aqueous solution causes only incomplete precipitation of the calcium as calcium sulphate, even on heating.

Dissolve 1 Gm. of calcium gluconate-Sandoz in 10 cc. of water; add 2 cc. of ammonia water and 5 cc. of ammonium oxalate: an immediate precipitation, which readily deposits on heating, results (*calcium*). To

1 cc. of a 10 per cent aqueous solution add 1 drop of ferric chloride: a canary yellow color is obtained (*a-oxyacid*). To 5 cc. of a 10 per cent aqueous solution add 0.65 cc. of glacial acetic acid and 1 cc. of phenylhydrazine (fresh) and heat the mixture on a steam bath for thirty minutes; allow to cool, and scratch the sides of the tube for a few seconds with a glass rod: a crystalline deposit of gluconic-acid-phenylhydrazide is formed. Filter the crystalline mass, and purify by dissolving in 10 to 15 cc. of hot water; add a small amount of charcoal and filter; allow the filtrate to cool: pure white crystals melting with decomposition at 200 to 202 C. are obtained.

To 5 cc. of a 3 per cent aqueous solution of calcium gluconate-Sandoz add 5 drops of nitric acid and 1 cc. of silver nitrate: not more than a slight opalescence appears (*chloride*). To 5 cc. of a 3 per cent aqueous solution add 2 cc. of alkaline cupric tartrate solution and boil: no reduction takes place (*glucose*). To 5 cc. of a 3 per cent aqueous solution add 5 drops of diluted hydrochloric acid and 1 cc. of barium chloride solution: no turbidity appears (*sulphate*). An aqueous solution meets the requirements of the U. S. P. tests for the absence of heavy metals (see U. S. P. X, p. 439).

Transfer about 0.2 Gm. of calcium gluconate-Sandoz, accurately weighed, to a large platinum crucible and moisten with 3 drops of olive oil; heat slowly and after carbonization heat the residue at red heat in an electric muffle furnace until it is completely white; bring the residue to constant weight: the residue represents not less than 12.4 nor more than 12.8 per cent of calcium oxide.

CALCIUM PEROXIDE.—See Peroxides, Metallic.

CAMIOFEN OINTMENT.—An ointment obtained by mixing iocamfen (a liquid obtained by the interaction of iodine 10 parts, phenol 20 parts and camphor 70 parts, containing about 7.25 per cent free iodine) with an equal weight of a mixture composed of lard, wax and oil of theobroma, but containing nearly all of its iodine in the combined form.

Actions and Uses.—The ointment has the properties of fatty iodine compounds, phenol and camphor.

It is used in various skin diseases, inflammatory swellings, itching, etc.

Dosage.—It is applied directly or on gauze, undiluted or mixed with fatty substances. The parts to which camiofen ointment is applied should be dry, and the application of mercuric chloride before or after the use of the ointment must be guarded against.

Prepared by Schering and Glatz, Inc., Bloomfield, N. J., and New York, N. Y. No U. S. patent. U. S. trademark 119,578.

CANTHARIDIN.—Cantharidinum.—$C_{10}H_{12}O_4$.—The inner anhydride (lactone) of cantharidic acid.

Actions and Uses.—Preparations of cantharidin are used in place of corresponding preparations of cantharides and have the advantage of being more cleanly and more uniform in strength. Cantharidin is recognized by the British, French and Swiss Pharmacopeias. Cantharidin is more toxic to the kidney when the urine is acid than when it is alkaline.

Dosage.—From 0.00025 to 0.0005 Gm. ($\frac{1}{240}$ to $\frac{1}{120}$ grain).

Cantharidin may be obtained from various species of *Cantharis* or of *Mylabris*. It may be prepared by digesting powdered cantharides with a mixture of concentrated sulphuric acid and acetic ether at ordinary temperature, then mixing with barium carbonate and exhausting the mixture with acetic ether. The solvent may be removed by distillation and the residue allowed then to stand for some time to allow the cantharidin to crystallize. The resulting crystals may be washed with petroleum benzin to remove the fat and then recrystallized from hot alcohol.

Cantharidin occurs as colorless glistening, inodorous crystals; 0.1 Gm. on incineration should leave no weighable residue. Cantharidin is very slightly soluble in water, petroleum benzin or alcohol (90 per cent; soluble in chloroform (1 in 65), in acetic ether (1 in 150), and in acetone (1 in 40), and is soluble also in fixed oils. A 0.1 per cent solution in a fixed oil raises blisters when kept in contact with the skin. The melting point is from 210 to 212 C. Cantharidin slowly volatilizes at 100 C., more rapidly at higher temperatures. It is soluble in solution of sodium hydroxide, the solution depositing crystals of cantharidin when acidified. Gently warmed with sulphuric acid it yields a colorless solution, from which it is separated unchanged when freely diluted with water.

Cantharidin-Merck.—A brand of cantharidin-N. N. R.
Merck & Co., Inc., Rahway, N. J., distributor.

CARBON TETRACHLORIDE.—For description see the U. S. Pharmacopeia under Carbonei Tetrachloridum.

Actions and Uses.—Carbon tetrachloride has narcotic and anesthetic properties somewhat similar to those of chloroform. It has recently come into use as a vermifuge in the treatment of hookworm disease. It also removes some intestinal parasites other than the hookworm, such as *Oxyuris vermicularis, Ascaris lumbricoides* and *Trichocephalus dispar*, but it is less effective against these worms than some other drugs, such as oil of chenopodium. It is reported that usually about 95 per cent of the hookworms are removed by the first dose of carbon tetrachloride and that occasionally all are removed. As a vermifuge it appears to be relatively safe, but serious symptoms and even death have been reported, especially in patients addicted to the use of alcohol. During treatment some of the patients complain of headache. Good results are obtained by administration in water or milk or in gelatin capsules on an empty stomach, followed in three hours by a purgative dose of magnesium sulphate. The capsules may be prepared extemporaneously. Lambert recommends giving the vermicide and a solution of magnesium sulphate together, claiming that this prevents headache. A mild laxative is generally given to constipated patients on the day previous to treatment. To insure complete removal of the hookworms a test dose of oil of chenopodium, 3 cc. (45 minims) may be given a week after the treatment with carbon tetrachloride. A second dose of carbon tetrachloride should not be given within three weeks. Alcohol should not be taken during treatment.

Dosage.—From 2 to 3 cc. (30 to 45 minims). Children 0.13 cc. (2 minims) for each year of age up to fifteen years.

If the drug is to be given with the purgative, the dose for adults is administered in 50 cc. (1½ fluidounces) of a solution of magnesium sulphate. For children the dose of the purgative is appropriately reduced. The dose of 3 cc. should not be exceeded.

Capsules Carbon Tetrachloride (For Human Use)-P. D. & Co., 20 minims. Each capsule contains carbon tetrachloride-U. S. P., 20 minims.

Prepared by Parke, Davis & Co., Detroit.

Capsules Carbon Tetrachloride-Mulford, 0.3 cc.
Prepared by the H. K. Mulford Co., Philadelphia, Pa.

Capsules Carbon Tetrachloride-Mulford, 1 cc.
Prepared by the H. K. Mulford Co., Philadelphia, Pa.

Capsules Carbon Tetrachloride-Mulford, 3 cc.
Prepared by the H. K. Mulford Co., Philadelphia, Pa.

CASCARA SAGRADA.—For description see the U. S. Pharmacopeia and Useful Drugs under Cascara Sagrada.

Borcherdt's Malt Extract with Cascara Sagrada: Each 100 cc. represents cascara sagrada 12.5 Gm. (60 grains per fluidounce) in Borcherdt's malt extract (plain) (which see under Extract of Malt).

Manufactured by Borcherdt Malt Extract Co., Chicago. No U. S. patent. U. S. trademarks 64,467 and 64,441.

Maltine with Cascara Sagrada.—Each hundred cc. represents cascara sagrada 12.5 Gm. (60 grains per fluidounce) in maltine (which see under Extract of Malt) as a vehicle.

Manufactured by The Maltine Company, Brooklyn. No U. S. patent. U. S. trademark 44,566.

CHAULMOOGRA DERIVATIVES

Chaulmoogra oil is a fixed (fatty) oil expressed from the seeds of *Taraktogenos kurzii,* a tree growing in Burma and adjacent countries. In addition to small quantities of the glycerides of the fatty acids commonly found in vegetable fats, chaulmoogra oil contains the glycerides of a series of highly unsaturated fatty acids, chiefly chaulmoogric acid, $C_{18}H_{32}O_2$, and hydnocarpic acid, $C_{16}H_{28}O_2$. This series of fatty acids differs from other ordinary fatty acids in being optically active and in possessing, as part of the molecular structure, a ring of carbon atoms. The therapeutic properties of chaulmoogra oil appear to be due to these optically active unsaturated fatty acids of the chaulmoogric series.

Chaulmoogra oil has been used in the treatment of leprosy for many years, the bulk of the evidence indicating that it is of value though not having specific, curative properties. The fatty acids of chaulmoogra oil have a destructive action on acid-fast bacilli, such as the bacillus of leprosy, and it is to this property that the beneficial effects of chaulmoogra oil derivatives in leprosy are probably due. Chaulmoogra oil is given by mouth or by hypodermic injection, although the latter procedure is not devoid of disadvantages (abscesses).

The sodium salts of the fatty acids of chaulmoogra oil and the ethyl esters prepared from these fatty acids have been introduced for hypodermic use in the treatment of leprosy with the claim that they are better tolerated than the oil. In India, preparations of the first kind have been used considerably and Leonard Rogers, in particular, reports the successful use of the sodium salts at first subcutaneously and later on intravenously. The ethyl esters prepared from the fatty acids of the oil have been used by several observers for a number of years. H. T. Hollmann, J. T. McDonald and A. L. Dean in Hawaii, by employing the esters by deep intramuscular injections, claim to have met with much greater success than had attended the work of others who had used the preparations earlier.

ETHYL CHAULMOOGRATE.—For description see the U. S. Pharmacopeia under Aethylis Chaulmoogras.

Actions and Uses.—See preceding article, Chaulmoogra Derivatives.

Dosage.—Orally, Ethyl Chaulmoograte is administered in gradually increasing doses of from 1 cc. to 5 cc. daily after meals with warm milk or hot tea. Intramuscularly, 1 cc. is the initial dose, this being increased by 1 cc. every second or third injection until a maximum of 3 cc. to 5 cc. is reached. The injections are administered once a week.

Chaulmestrol.—A brand of ethyl chaulmoograte-U. S. P.

Manufactured by The Bayer Company, Inc., Rensselaer, N. Y. (Winthrop Chemical Co., New York, distributor). U. S. patent 957,633 (May 10, 1910; expires 1927). U. S. trademark 155,565.

Ampules Chaulmestrol, 1 Cc.
Ampules Chaulmestrol, 3 Cc.

CHINOSOL.—Oxyquinolin Sulphate.—$(C_9H_7ON)_2H_2SO_4$.—A normal oxyquinolin sulphate.

Actions and Uses.—So far as experimental evidence and experience go, chinosol is nontoxic. It is a powerful antiseptic, somewhat stronger in this respect than mercuric chloride and considerably stronger than phenol. It has been found to exert an antiseptic action in 1 in 10,000 solutions. It is a feeble germicide, being weaker than phenol and much weaker than mercuric chloride. It is incompatible with alkaline substances (soap) and with salts of mercury and iron. Chinosol does not coagulate albumin or injure the mucous membranes or tissues. The sensitiveness of patients to its solution varies considerably. In some, it produces a pronounced stinging when applied to mucous membranes even in dilute solutions (1 in 2,000), but it is claimed not to cause harmful irritation in any strength. The 1 in 1,000 solution has no analgesic action, while in 5 per cent powder form such action is present. Chinosol is claimed to be an efficient deodorant.

Dosage.—For internal use, 0.3 Gm. (5 grains) three times daily. As an antiseptic, the average strength of solution used is 1 in 1,000; as a nasal spray or douche, 1 in 3,000; as a gargle, 1 in 2,000, and as an eye-wash, 1 in 4,000, gradually increased in each case according to the tolerance of the patient up to 1 in 500. In gargles the strength may be increased to 1 in 250. As a vaginal douche the initial strength used is 1 in 1,000, increased to 1 in 100 if necessary.

Manufactured by Chinosol Company, New York (Parmele Pharmacal Company, New York, distributor). U. S. patent 906,918 (Dec. 15, 1908; expired). **U. S. trademark 28,750.**

Chinosol Tablets: **Each contains chinosol 0.5 Gm.**

Chinosol is a yellow crystalline powder of saffron-like odor and burning taste. It melts at from 175 to 177.5 C. It dissolves readily in water, but with difficulty in alcohol, and it is insoluble in ether. The aqueous solution has an acid reaction.

A drop of ferric chloride solution produces in a solution of chinosol a marked green coloration. Barium chloride solution produces a white precipitate. Solutions of alkaline hydroxides precipitate from an aqueous solution of chinosol a white precipitate, consisting of interlaced crystalline needles, which, after filtration, washing and careful drying in a desiccator, should melt at from 73 to 75 C. On incineration, chinosol should not leave a weighable residue.

CHLORAL DERIVATIVES AND SUBSTITUTES

Chloral is still the standard hypnotic of its class; but it has the disadvantage of causing cardiac and respiratory depression in overdosage and of irritating the stomach unless diluted suitably; furthermore, it cannot be used hypodermically. Attempts to modify the drug so as to make it safer have at the same time resulted in weakening its hypnotic action. Attempts to remove its irritant action have been more successful. The following chloral derivatives are described below and include several preparations which are less irritating to the stomach, and at least one which can be given by hypodermic injection (chlorbutanol):

Butylchoral hydrate, trichlorbutylidene glycol, $CH_3CHCl.CCl_2.CH.(OH)_2$.

Chlorbutanol (chloretone), 1,1,1-trichlor-2-methylpropan-2-ol, $CCl_3.C(OH)(CH_3).CH_3$.

Chloralformamide (chloralamid) $CCl_3CH(OH)NH.COH$.

BUTYLCHLORAL HYDRATE.—Butylchloral Hydratum.—Trichlorbutylidene Glycol.—Croton Chloral Hydrate.—2,2,3-trichlorbutan-1, 1-di-ol.—$CH_3CHCl.CCl_2.CH(OH)_2$.—A crystalline product obtained by the addition of water to liquid butyl chloral (2,2,3-trichlorbutanol, $CH_3CHClCCl_2.CHO$).

Actions and Uses.—The action of this preparation is similar to that of chloral, except that the former is said to be less depressing and more analgesic. It has been especially recommended for relief of facial neuralgia.

Dosage.—From 0.3 to 1.3 Gm. (5 to 20 grains).

Butyl-chloral hydrate occurs in pearly white, trimetric laminae, having a pungent but not acrid odor, and an acrid, nauseous taste. It fuses at about 78 C. to a transparent liquid, which, in cooling, begins to solidify at about 71 C. It is soluble in about 50 parts of water, and in its own weight of glycerin or of alcohol (90 per cent); it slowly dissolves in 20 parts of chloroform. From a solution in alcohol, it is precipitated by the gradual addition of water in the form of globules said to consist of butylchloral alcoholate, $C_4H_5Cl_3O.C_2H_5OH$. The alcoholic solution is neutral, and the aqueous solution is neutral or but slightly acid to litmus.

It gives no precipitate with solution of silver nitrate. Heat about 0.2 Gm. of butyl-chloral hydrate with 10 cc. of sodium hydroxide solution and add 2 drops of a saturated aqueous solution of aniline: the odor of phenyl isocyanide is not evolved (*chloral hydrate*).

Butyl-Chloral Hydrate-Merck. — A brand of butylchloral hydrate-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.

CHLORBUTANOL.—Chlorbutanol.—Trichlortertiarybutyl-alcohol. — Acetonechloroform. — $CCl_3.C(OH).CH_3.CH_3$—1,1,1-trichlor-2-methylpropan-2-ol, produced by the reaction of acetone on chloroform.

Actions and Uses. — Chlorbutanol is said to be absorbed unchanged from the alimentary tract, but to be decomposed in the body. It is a local anesthetic with an action weaker than that of cocaine, but sufficient frequently to prevent vomiting from gastric irritation. Its antiseptic action is said to be fifteen times as strong as that of boric acid. It acts on the central nervous system similarly to chloral, and although the claim has been made that hypnotic doses are without effect on the circulation and respiration, independent observers have described a fall of blood pressure and interference with respiration in animals, and consider it fully as dangerous as chloral. In man, 100 grains (6.5 gm.) caused severe symptoms, but recovery occurred. It is claimed that no habit is induced, but this may be because of its restricted employment. It is said to be useful as a mild local anesthetic in dentistry, etc., as a preservative for hypodermic solutions, for insomnia, vomiting, and for spasmodic conditions. It is also said to be useful as an introductory to general anesthesia, as it lessens excitement and nausea.

Dosage.—From 0.3 to 1.3 Gm. (5 to 20 grains) dry or in capsules. Hypodermically as a local anesthetic a saturated aqueous solution may be used.

Chlorbutanol is a white, crystalline, volatile compound, having a camphoraceous odor and taste. It is soluble in water (8 in 1,000), in fixed and volatile oils, and glycerin; very soluble in alcohol, ether, benzin, glacial acetic acid, chloroform, and acetone.

Chloretone.—A brand of chlorbutanol-N. N. R.

Manufactured by Parke, Davis & Company, Detroit. U. S. trademark.

Boro-Chloretone: A dusting powder composed of chloretone, 1 part; boric acid, 1 part; purified talc, 2 parts.

Chloretone Capsules, 3 grains.

Chloretone Capsules, 5 grains.

Chloretone Inhalant: Chloretone, 1 Gm.; camphor, 2.5 Gm.; menthol, 2.5 Gm.; oil of cinnamon, 0.25 Gm.; refined liquid petrolatum, 93.75 Gm.

CHLORINATED PARAFFIN.—For description see the U. S. Pharmacopeia under Paraffinum Chlorinatum.

Actions and Uses.—The chlorine of chlorinated paraffin is therapeutically without action. Chlorinated paraffin is used as a solvent for dichloramine. With it, solutions containing up to 8 per cent may be prepared. The high viscosity of the oil prevents its being readily sprayed with a hand spray; the addition of about 10 per cent carbon tetrachloride will reduce the viscosity so that it can be readily sprayed in an ordinary oil atomizer.

CINCHOPHEN AND CINCHOPHEN DERIVATIVES

Cinchophen was introduced in therapeutics under the proprietary name "atophan." It was admitted to the U. S. Pharmacopeia as Acidum Phenylcinchoninicum, the name being later changed to cinchophenum. Cinchophen and its compounds are derived from quinolin carboxylic acid. Cinchophen is phenylquinolincarboxylic acid. Neocinchophen (introduced as novatophan) is ethylmethylphenylquinolincarboxylic acid. Cinchophen has a slightly bitter taste, while neocinchophen is practically tasteless; otherwise their actions are closely similar.

Actions and Uses.—Cinchophen and cinchophen derivatives increase the permeability of the kidneys selectively to uric acid, and therefore greatly increase the excretion of the urates. Under a purin-free diet the amount of uric acid in the blood is reduced one half; when exogenous purins are given, the total amount is rapidly excreted so that the content of uric acid in the blood remains at normal or below. The influence of cinchophen on uric acid excretion is greater and is exerted more promptly than that of sodium salicylate. Its action grows weaker after the first three hours and is practically terminated in nine hours after the administration of the dose. The amount of ammonia and that of total nitrogen in the urine are slightly increased during the action of cinchophen, but not in proportion to the increase in the uric acid of the urine. Cinchophen does not increase the leukocytes, the purin bases or the phosphoric acid. There is no evidence of increased formation of uric acid or of any effect on deposited urates.

Cinchophen is useful in acute gout; it relieves pain in this disease, acting more promptly than colchicum and, when proper dosage is used, generally without undesirable by-effects. In nonuratic joint affections, particularly acute articular rheumatism, favorable results are reported, while the chronic forms seem to yield to cinchophen only in isolated cases. It frequently relieves the pain of sciatica, but not invariably according to McLester (*Arch. Int. Med.* **12**:739 [Dec.] 1913).

While cinchophen is relatively harmless in suitable doses, overdosage results in various symptoms of intoxication. Among these are a sense of oppression in the gastric region with acid eructation and diarrhea, which can be avoided by the simultaneous use of small doses of sodium bicarbonate. In cystitis it may cause pain in the bladder with hematuria. It occasionally induces a scarlet, an urticaria-like, or a vesiculous rash. It sometimes induces cardiac distress with dizziness. Excessive doses or the long continued use of moderate amounts may cause damage to the kidney and occasionally gives rise to acute yellow atrophy or to dangerous or fatal hepatitis, usually characterized by the late and relatively abrupt onset of symptoms, the most frequent being jaundice. The appearance of skin rash, vomiting, anorexia, albuminuria, heartburn, diarrhea or jaundice requires the immediate discontinuance of the drug. Relatively small doses occasionally induce symptoms in patients showing idiosyncrasy, and it is possible that an attack of hepatitis renders the patient extremely susceptible to further medication at a later date. Especial caution is necessary in the use of cinchophen in the presence of renal insufficiency. The promiscuous use of cinchophen by the public for the relief of pain is obviously dangerous.

Dosage.—In gout the dose of cinchophen is from 0.5 Gm. (8 grains) four times a day to 1 Gm. (15 grains) three times a day suspended in large quantities of water. In order to prevent the precipitation of free uric acid from the urine with possibly resulting renal colic, Weintraud considers it necessary to administer simultaneously 15 Gm. (225 grains) of sodium bicarbonate in the course of the first day and from 5 to 10 Gm. (75 to 150 grains) on the following days. In articular rheumatism, Heller prescribes daily doses of from 3 to 5 Gm. (45 to 75 grains).

2-phenyl-quinolin-4-carboxylic acid was described by Doebner and Giesecke in 1887 (*Ann. d. Chem.* **242**: 291, 1887), who prepared it by warming together pyroracemic acid, benzaldehyde and anilin in alcoholic solution. Its therapeutic action was described by Nicolaier and Dohrn in 1908 (*Deutsch. Arch. f. klin. Med.* **93**: 331, 1908).

ATOQUINOL-CIBA.—Allyl-2-phenyl-quinolin-4-carboxylate. The allyl ester of 2-phenyl-quinolin-4-carboxylic acid. $C_9H_5N.\ C_6H_5COOC_3H_5$ 2:4.

Actions and Uses.—The actions and uses of atoquinol-Ciba are practically like those of cinchophen.

Dosage.—Four to eight tablets in 24 hours, taken after meals, with abundance of water. Twelve tablets may be taken daily for a short time if necessary for the relief of severe pain, but as soon as the active symptoms subside, the dose should be reduced to three to five tablets daily for three days in every week or in alternate weeks. Sodium bicarbonate, 0.6 to 2.0 Gm. (10 to 30 grains) should be administered with atoquinol-Ciba to avoid renal irritation from an excess of uric acid or urates.

Manufactured by the Society of Chemical Industry in Basle, Switzerland (Ciba Company, Inc., New York). U. S. patent 1,336,952 (April 13, 1920; expires 1937). U. S. trademark 142,139.

Tablets Atoquinol 0.25 Gm. (4 grains).

Atoquinol occurs as a yellow, granular, odorless powder, with an aromatic taste; readily soluble in alcohol, about 1 in 12.5; easily soluble in ether, acetone, benzene and fatty oils; insoluble in water. A saturated aqueous solution is neutral to litmus. It melts at not less than 36 C.

Heat about 0.3 Gm. of atoquinol with an equal portion of sodium sulphide crystals: it is decomposed with the evolution of alliaceous odor. Dissolve about 1 Gm. in 25 cc. of alcohol, add 20 cc. of alcoholic potassium hydroxide solution and reflux on a steam-bath for 30 minutes, remove the excess of alcohol by evaporating on the steam-bath, dissolve the residue in 100 cc. of warm water, add diluted acetic acid until no further precipitate is formed, cool; collect the precipitate on a filter-paper, wash with water until it is free from acetic acid; dry at 100 C.: this precipitate responds to U. S. P. X tests for cinchophen. Heat about 0.5 Gm. with 10 cc. of ammonia water: the substance does not dissolve (*distinction from cinchophen*). Dissolve about 0.01 Gm. in 10 cc. of alcohol, add 5 drops of ferric chloride solution: a yellow color results (*distinction from cinchophen,* which produces a reddish brown color). Boil 0.1 Gm. with 0.5 cc. of sodium hydroxide solution and add 5 cc. of iodine solution: no odor develops (*distinction from neocinchophen,* which emits an odor of iodoform).

Boil 0.5 Gm. of atoquinol with 50 cc. of water for two minutes; no odor develops; cool and filter: separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulphate*); no coloration or precipitation on saturation with hydrogen sulphide (*salts of heavy metals*).

Incinerate about 1 Gm. of atoquinol, accurately weighed: the residue is not more than 0.1 per cent. Dissolve about 1 Gm., accurately weighed, in 50 cc. of previously neutralized alcohol; add 25 cc. of half-normal alcoholic potassium hydroxide solution; allow to stand for 30 minutes at 20 C., occasionally agitating and titrate the excess of alkali with normal hydrochloric acid, using phenolphthalein as an indicator: the amount of half-normal potassium hydroxide solution consumed corresponds to not less than 86 per cent nor more than 89 per cent, cinchophen.

CINCHOPHEN.—Cinchophenum.—For description see the U. S. Pharmacopeia and Useful Drugs.

Actions, Uses and Dosage.—See preceding article, Cinchophen and Cinchophen Derivatives.

Tablets Cinchophen-Abbott, 5 grains.

Tablets Cinchophen-Abbott, 7½ grains.

Prepared by the Abbott Laboratories, North Chicago.

Cinchophen-Calco Tablets, 7½ grains.

Prepared by the Calco Chemical Company, Bound Brook, N. J.

Tablets Cinchophen-Morgenstern: Each contains cinchophen-Morgenstern 0.5 Gm. (7.5 grains).

Cinchophen Water-Morgenstern: A solution of sodium phenylcinchoninate containing sodium bicarbonate and sweetened with sugar, representing the equivalent of 1 Gm. (15 grains) cinchophen-Morgenstern per fluidounce. It is prepared by dissolving cinchophen-Morgenstern 15 Gm., sodium bicarbonate 11.7 Gm., and sugar 90 Gm. in water enough to make 450 cc.

Prepared by Morgenstern & Co., New York.

CHLOROXYL.—Phenylcinchoninic acid hydrochloride.—$C_6H_5C_9H_5NCOOH.HCl$. The hydrochloride of 2-phenylquinolin-4-carboxylic acid.

Actions, Uses and Dosage.—The same as those of cinchophen.

Manufactured by Eli Lilly & Company, Indianapolis, Ind. U. S. patent 1,306,439 (June 10, 1919; expires 1936). U. S. trademark 123,336.

Chloroxyl Tablets, 5 grains.

Chloroxyl is a yellow crystalline powder with an astringent, slightly bitter taste. It is insoluble in water, ether or chloroform, but slightly soluble in alcohol.

Accurately weigh about 2 Gm. of chloroxyl, add 50 cc. of half-normal sodium hydroxide and heat on a boiling water bath for one hour. Determine the excess of sodium hydroxide by titration with half-normal hydrochloric acid solution, using phenolphthalein as indicator: chloroxyl contains not less than 11.5 per cent nor more than 12.5 per cent of combined hydrochloric acid (each cc. sodium hydroxide solution is equivalent to 0.00912 Gm. HCl).

Dissolve 2 Gm. chloroxyl in 10 cc. sodium hydroxide solution; heat to boiling, and while hot add acetic acid until no further precipitate is formed. Cool, decant the supernatant liquid and wash the precipitate with distilled water until it is free from acetic acid. Dry the precipitate at 100 C.: this precipitate responds to the U. S. P. tests for phenylcinchoninic acid.

NEOCINCHOPHEN.—Neocinchophenum.—Ethyl-6-methyl-2-phenyl-quinolin-4-carboxylate, the ethyl ester of methyl-phenyl-quinolin-carboxylic acid. — $CH_3C_9H_4N.C_6H_5COOC_2H_5$, 6:2:4. Neocinchophen was first introduced as novatophan.

Actions and Uses.—The same as those of cinchophen. See preceding general article, Cinchophen and Cinchophen Derivatives.

Dosage.—The same as that of cinchophen. Neocinchophen is practically tasteless.

Neocinchophen is a pale, yellow, crystalline powder; odorless and tasteless; permanent in the air. It is nearly insoluble in water and in dilute alkalis; soluble in hot alcohol and in strong acids; very soluble in ether and in chloroform. The melting point of neocinchophen is not below 74 C. Boil 0.1 Gm. of neocinchophen with 0.5 cc. of sodium hydroxide solution and add 5 cc. of iodine solution: the odor of iodoform is apparent. Dissolve 0.1 Gm. of neocinchophen in 1 cc. of sulphuric acid and add bromine water drop by drop until an excess has been added: a yellow precipitate results. Boil 0.1 Gm. of neocinchophen with 1 cc. of hydrochloric acid, filter while hot and add a few drops of platinic chloride solution: a yellow, crystalline precipitate results. Add a few drops of ferric chloride solution to an alcoholic solution of neocinchophen (1 in 100): a yellow color is produced (*distinction from cinchophen*, which produces a reddish brown color). Warm about 0.5 Gm. of neocinchophen in 10 cc. of ammonia water: the substance does not dissolve (*distinction from cinchophen*).

Incinerate about 0.5 Gm. of neocinchophen, accurately weighed: not more than 0.1 per cent of residue remains.

Neocinchophen-Abbott.—A brand of neocinchophen-N. N. R.

Manufactured by The Abbott Laboratories, North Chicago, under U. S. patent 1,045,759 (Nov. 26, 1912; expires 1929), by license of The Chemical Foundation, Inc.

Neocinchophen-Abbott Tablets, 5 grains.

Neocinchophen-B. P. C.—A brand of neocinchophen-N. N. R.

Manufactured by Benzol Products Company, Newark, N. J., under U. S. patent 1,045,759 (Nov. 26, 1912; expires 1929), by license of The Chemical Foundation, Inc.

CHINIOFON. — Sodium-iodoxyquinolinesulphonate. — A mixture prepared from approximately four parts of 7-iodo-8-hydroxy-quinoline-5-sulphonic acid, containing not less than 26.5 per cent of combined iodine, and 1 part of sodium bicarbonate. After preparation there is generally some chemical reaction, so that the product may contain a small amount of sodium iodohydroxyquinolinesulphonate in addition to the sodium bicarbonate and the uncombined iodohydroxyquinolinesulphonic acid. On dissolving the product in water, 100 parts of chiniofon yield approximately 85 parts of sodium iodohydroxyquinolinesulphonate.

Actions and Uses.—Chiniofon, which is closely similar to preparations introduced under various proprietary names as wound antiseptics, has been found to be of use in the treatment of amebic dysentery. It is claimed that the action of the drug is probably due to its absorption and direct action through the blood stream on the amebas invading the bowel wall. The drug has been reported in some cases to produce diarrhea; but serious toxic effects do not appear to be common.

Dosage.—Orally, for adults, from 0.25 to 1.0 Gm. (4 to 15 grains) in the form of pills, cachets or solution, three times daily; for children, according to age; rectally, 1 to 5 Gm. (15 to 75 grains) freshly dissolved in 200 cc. of water at a temperature not exceeding 44 C. The course of treatment requires from seven to fourteen days. Combined oral and rectal administration has been used in acute cases and in the more serious chronic cases accompanied by obstinate clinical symptoms. It has been pointed out that the iodine content of chiniofon should be considered when chronic endamebiasis is accompanied by thyroid disturbance.

Chiniofon appears as a canary yellow powder with no odor, or only faint odor, and possessing a bitter taste, but leaving later a distinctly sweetish after-taste. It dissolves in water with effervescence due to the reaction of the uncombined sodium bicarbonate and iodohydroxyquinolinesulphonic acid. The sodium salt is soluble in water to the extent of about 4 per cent; is insoluble in alcohol, ether, chloroform and most of the organic solvents. Chiniofon is decomposed at 223 C.; a solution of chiniofon decomposes on boiling. The addition of strong acids changes the color to pale green and liberates free iodohydroxyquinolinesulphonic acid. To 10 cc. of the solution of chiniofon 1 per cent add five drops of ferric chloride solution: a deep emerald green color forms. To 10 cc. of chiniofon solution 1 per cent add 5 cc. of copper sulphate solution: a dense white precipitate forms. Agitate 5 cc. of aqueous solution of chiniofon 1 per cent made slightly acid with diluted hydrochloric acid with 5 cc. of chloroform: no violet color appears in the chloroform (*iodine*). Acidify 5 cc. of a solution of chiniofon 1 per cent with hydrochloric acid, underlay with chloroform, and add one drop of sodium nitrite solution: the chloroform assumes the characteristic iodine color. To 5 cc. of a solution of chiniofon 1 per cent add 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution: a faint opalescence is apparent.

To about 1.5 Gm. of chiniofon accurately weighed into a small beaker add all at once and with rapid rotation 15 cc. of a solution of 10 cc. diethylamine in 90 cc. of anhydrous methyl alcohol. Decant the solution from the insoluble material onto a small filter moistened with anhydrous methyl alcohol. Collect the clear filtrate and subsequent washings in a porcelain dish of about 200 cc. capacity. Wash the precipitate, beaker, filter and funnel carefully with anhydrous alcohol until no trace of color is imparted to the alcohol. Allow the surplus alcohol to evaporate from the beaker and funnel, add 25 cc. of distilled water to the beaker, pass the solution through the funnel collecting the filtrate in a 250 cc. flask. Wash the beaker and funnel with separate small portions of water until all bicarbonate is dissolved; add to the solution methyl orange and titrate the bicarbonate with tenth-normal acid. The volume of tenth-normal acid used should indicate not less than 18 per cent sodium bicarbonate nor more than 22 per cent sodium bicarbonate.

To about 0.200 Gm. of chiniofon accurately weighed into a 35 cc. nickel crucible, add about 3 Gm. of anhydrous sodium carbonate. Moisten the mixture thoroughly with water, fill the crucible about three-fourths full with anhydrous sodium carbonate and apply the heat of a Bunsen burner. Heat carefully at first to avoid loss and finally to dull redness for five minutes. Allow the mixture to cool, place the crucible with contents in a 250 cc. beaker and add about 50 cc. of distilled water. When the mass is well disintegrated, pass the solution through a well wetted filter and collect the filtrate in a 500 cc. flask. Wash the crucible, beaker, funnel, etc., well with small portions of distilled water until the filtrate is neutral to litmus paper. Heat the clear filtrate to near 100 C.; add potassium permanganate solution until a permanent purple color remains even after two or three minutes' heating. Add to the hot mixture a few drops of ethyl alcohol to remove the purple color and filter the hot liquid collecting the filtrate in a 500 cc. flask. Wash the precipitate, filter, etc., until the washings are neutral to litmus paper, cool the solution and add sulphuric acid to distinct acid reaction, taking care to avoid loss from effervescence. To the acid liquid add a solution of 2 Gm. of potassium iodide, free from iodate, and titrate the liberated iodine with tenth-normal sodium thiosulphate solution. The volume of tenth-normal sodium thiosulphate used should indicate not less than 26.5 per cent iodine, nor more than 28.9 per cent iodine.

CITRESIA.—Magnesium Acid Citrate.—$MgHC_6H_5O_7.5H_2O$.—Citresia is the hydrated acid magnesium salt of citric acid containing not less than 98 per cent of $MgHC_6H_5O_7.5H_2O$.

Actions and Uses.—Citresia has the laxative and purgative action of magnesium citrate.

Dosage.—As a laxative 25 Gm. (6 drachms); as a purgative 50 Gm. (1½ ounces). It may be administered by dissolving citresia 25 Gm. in syrup of citric acid 25 cc. and water enough to make 150 cc.

Manufactured by Horace North, Brooklyn, N. Y. No U. S. patent or trademark.

Citresia is a white or faintly yellowish-white, crystalline, odorless substance having a pleasant acidulous taste. Citresia is very soluble in water; insoluble in alcohol, ether or chloroform. Five Gm. of citresia should dissolve without residue in 25 cc. of water.

If to 10 cc. of an aqueous solution of citresia (1 in 20) 1 cc. of hydrochloric acid and 1 cc. of sodium phosphate solution be added and the solution be made slightly alkaline with ammonia water, a white, crystalline precipitate should be produced. If 10 cc. of the aqueous solution of citresia (1 in 20) is neutralized with potassium hydroxide solution and 1 cc. of calcium chloride solution added, no precipitate is produced. After boiling the mixture for one or two minutes, a white, crystalline precipitate should appear. If 5 Gm. of citresia is shaken with 25 cc. of alcohol, the mixture filtered, the filtrate evaporated, the residue, if any, dried for one hour at 100 C., and weighed, the weight found does not amount to more than 0.05 Gm. (limit of *citric acid, and some other impurities*). If from 0.5 Gm. to 0.8 Gm. of citresia is weighed, and the salt dried to constant weight at 75 C., the loss does not amount to more than 30 per cent (*absence of an undue amount of water*).

If from 0.5 Gm. to 0.8 Gm. of citresia is weighed, the salt ignited and the residue weighed, the ash amounts to not less than 13 per cent.

If from 2 Gm. to 3 Gm. of citresia is weighed, the salt dissolved in 25 cc. of water and the cold solution titrated with normal potassium hydroxide, using phenolphthalein as indicator, the alkali required should correspond to at least 98 per cent of hydrated magnesium acid citrate.

If from 0.5 Gm. to 0.8 Gm. of citresia is weighed, the salt dissolved in 50 cc. of 1 per cent hydrochloric acid, a slight excess each of sodium phosphate solution and ammonia water added, the mixture allowed to stand 15 hours, the precipitate collected in a weighed Gooch crucible, washed, dried, heated and weighed in the usual way, the weight of magnesium pyrophosphate corresponds to not less than 98 per cent of hydrated magnesium acid citrate ($MgHC_6H_5O_7 \cdot 5H_2O$).

COPPER SALTS

COPPER CITRATE.—Cuprum Citricum.—Cupric Citrate.—The cupric salt of citric acid, containing from 34 to 36 per cent of copper.

Actions, Uses and Dosage.—Copper citrate possesses the astringent and antiseptic properties of other salts of copper somewhat modified by its sparing solubility.

It may be used for the same purposes as, and in doses similar to, those of other salts of copper.

Copper Citrate Ointment (5 per cent.)-M. E. S. Co.: An ointment containing 5 per cent of copper citrate and 95 per cent of white petrolatum, without alcohol or preservative.

Copper Citrate Ointment (10 per cent.)-M. E. S. Co.: An ointment containing 10 per cent of copper citrate and 90 per cent of white petrolatum, without alcohol or preservative.

Manufactured by the Manhattan Eye Salve Company, Louisville, Ky. No U. S. patent or trademark.

Copper citrate occurs as a green or bluish-green, finely crystalline, odorless powder. It is but slightly soluble in cold water; somewhat more soluble in a cold solution of an alkali citrate, forming a greenish-blue solution; more soluble in a hot solution of an alkali citrate; also soluble in decomposition in ammonia water and in mineral salts.

When dissolved in ammonia water, copper citrate yields an intense blue solution. When heated to 90 C., the salt loses water of hydration and assumes a pale blue color. At a higher temperature, it blackens and at a low red heat leaves a black residue of cupric oxide. If about 1 Gm. of copper citrate is dissolved in 20 cc. of diluted hydrochloric acid, the solution diluted to 200 cc. with hot water, the mixture saturated with hydrogen sulphide, filtered, and the filtrate evaporated nearly to dryness on the water bath, the residue responds to the usual tests for citric acid. If 0.5 Gm. of copper citrate is dissolved in 10 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution added, no immediate turbidity occurs. A solution of 0.5 Gm. of the salt in 10 cc. of diluted sulphuric acid should not evolve any odor of acetic acid when boiled. The salt should be free from nitrates, chlorides and carbonates.

To about 0.5 Gm. accurately weighed, add 25 cc. water and 10 cc. of normal sulphuric acid. Heat the mixture almost to boiling until solution is complete, adding a little more acid if necessary. Cool the solution and add 10 cc. of potassium iodide solution and allow it to stand five minutes, with occasional shaking. Add 200 cc. of water and titrate the liberated iodine with tenth-normal sodium thiosulphate: the titration should indicate not less than 34 per cent copper.

Copper Citrate-Mallinckrodt.—A brand of copper citrate-N. N. R.

Manufactured by Mallinckrodt Chemical Works, St. Louis. No U. S. patent or trademark.

Copper Citrate-Merck.—A brand of copper citrate-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

CUPRIC SULPHATE.—For description see the U. S. Pharmacopeia and Useful Drugs under Cupri Sulphas.

Cupricsticks, Cupric Applicators and Special Cupric Applicators (Copper Sulphate 20-25 per cent.): Wooden sticks, 3.8, 14.0, 16.5 and 30.4 (1½, 5½, 6½ and 12 inches) long, respectively, tipped with a mixture of copper sulphate, alum and potassium nitrate, containing from 20 to 25 per cent of copper sulphate. Each stick to be used but once.

Prepared by Tappan Zee Surgical Company, Nyack, N. Y. No U. S. patent or trademark.

CREOSOTE AND GUAIACOL COMPOUNDS

Creosote consists of phenols and phenol derivatives, chiefly guaiacol and creosol. These have essentially similar antiseptic actions, resembling phenol. Creosote and guaiacol are used internally as intestinal and urinary antiseptics (see general article, Naphthol Compounds), as stimulant expectorants in bronchitis and in the treatment of tuberculosis. (Their efficiency in tuberculosis is still debatable.)

Their local irritant actions often interfere with their internal administration. This local action and the toxicity can be minimized, as with other phenols, by masking the active OH group, through replacement of its H by acid radicals, as in the official guaiacol carbonate and in most of the proprietary derivatives. These esters are insoluble and inactive, but like phenyl salicylate, are saponified in the intestines, liberating their active constituents gradually. These various esters are practically equivalent.

Note.—The Council wishes it understood that any claims of nontoxicity that are made for drugs that have or are supposed to have important general effects are admitted to this book only when they do not conflict with known facts. In all such instances, however, it is recommended that a claim of lack of toxicity be not accepted too freely, but be considered to mean only that toxic effects have not as yet been recognized with the doses that have been studied. The most sincere and apparently justified beliefs concerning this point are often ultimately reversed by extended experience. Much the same may be said regarding any claims that drugs are nonirritating.

CALCREOSE.—Calcium Creosotate.—A mixture containing in loose chemical combination approximately equal weights of creosote and lime.

Actions and Uses.—Calcreose, when administered internally, is claimed to have the same actions and uses as creosote. It is claimed that calcreose does not readily produce gastric distress, nausea and vomiting.

There is some evidence to indicate that by the use of calcreose, relatively large quantities of creosote may be administered, but it appears probable that such tolerance is due to the slower absorption and excretion and therefore decreased efficiency. That the creosote contained in calcreose is liberated in the body is evident from the fact that during its elimination by the kidneys it has produced albuminuria and phenol urine.

Dosage.—From 0.25 to 1 Gm. (4 to 16 grains) every two to four hours, beginning with small doses and gradually increasing until tolerance is reached. Calcreose may be given in the form of calcreose solution or as tablets.

Manufactured by The Maltbie Chemical Company, Newark, N. J. U. S. patent 1,047,961 (Dec. 24, 1912; expires 1929). U. S. trademark 94,789.

Calcreose Tablets, 4 grains.

Compound Syrup of Calcreose.—A syrup containing in 100 cc. calcreose solution, 33.3 cc.; alcohol, 5 cc.; extractives from wild cherry, 4 Gm. (20 grains per fluidounce); chloroform, 0.6 cc. (3 minims per fluidounce); peppermint and other aromatic drugs.

Dosage.—Four to 8 cc. (1 to 2 fluidrachms).

Solution Calcreose: Prepared by adding 454 Gm. (1 pound avoirdupois) calcreose to 3,785 cc. (1 gallon) of water, agitating occasionally during twenty-four hours, filtering and adding enough water through the filter to make 3,785 cc. (1 gallon) of solution.

Dosage.—Four to 8 cc. (2 to 4 fluidrachms) in a half glass of water, followed immediately by one-half glass of water, beginning with 4 cc. (1 fluidrachm) in one-fourth glass of water.

According to the patent specifications, calcreose is made by the interaction of equal parts of creosote and lime in the presence of water. A minute quantity of phenolphthalein is added to the finished product to improve the color of calcreose solution.

Calcreose is a dark brown powder, having an empyreumatic odor and a sharp phenolic taste. It is partially soluble in water; the alkaline solution containing calcium compounds of the phenolic bodies of creosote while the insoluble portion consists largely of calcium hydroxide and calcium carbonate.

CREOSOTE.—For description see the U. S. Pharmacopeia and Useful Drugs under Creosotum.

Borcherdt's Malt Extract with Creosote: Each 100 cc. contains creosote, U. S. P., 0.83 cc. (4 minims per fluidounce) in Borcherdt's malt extract (plain) (which see under Extract of Malt).

Manufactured by Borcherdt Malt Extract Co., Chicago. No U. S. patent. U. S. trademarks 64,467 and 64,441.

Maltine with Creosote: Each hundred cc. represents creosote-U. S. P., 0.83 cc. (4 minims per fluidounce) in maltine (which see under Extract of Malt) as a vehicle.

Manufactured by The Maltine Company, Brooklyn. No U. S. patent. U. S. trademark 44,566.

CREOSOTE CARBONATE.—For description see the U. S. Pharmacopeia under Creosoti Carbonas.

Creosotal-Winthrop. — A brand of creosote carbonate-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent expired.

GUAIACOL BENZOATE.—**Guaiacolis Benzoas.**—Benzosol. $C_6H_5COO.C_6H_4.OCH_3$.—Guaiacol Benzoate is the benzoic acid ester of guaiacol.

Actions and Uses.—Guaiacol benzoate is decomposed slowly in the intestinal tract into guaiacol and benzoic acid, which exert their usual actions. The liberated constituents are absorbed and excreted in the urine. It is claimed to be non-irritating.

Its uses are analogous to those of creosote and of benzoic acid. It is said to be useful in incipient pulmonary tuberculosis, as an intestinal antiseptic in fermentation, diarrhea, typhoid fever, diabetes mellitus and as a urinary antiseptic in cystitis, etc. (See general article, Naphthol Compounds.)

Dosage.—From 0.2 to 0.6 Gm. (3 to 10 grains), in powder, capsule, pill, or suspended in liquids or as an emulsion.

Guaiacol benzoate occurs in minute colorless crystals; odorless or having a faint aromatic odor; tasteless or nearly so. Guaiacol benzoate is almost insoluble in water; soluble in ether and chloroform; also soluble in hot alcohol. Guaiacol benzoate melts at from 59 to 61 C.

With sulphuric acid guaiacol benzoate forms a permanent yellow coloration. Ferric chloride produces in the guaiacol benzoate-sulphuric acid mixture a violet color, changing to green and blue, and on the further addition of nitric acid, to orange and green, or of potassium nitrite to green, violet and yellow.

On heating with alcoholic potassium hydroxide guaiacol benzoate is saponified and the odor of guaiacol is developed.

Guaiacol benzoate is incompatible with the alkalies, which split it into guaiacol and benzoic acid.

Incinerate about 1 Gm. of guaiacol benzoate, accurately weighed: The ash does not exceed 0.1 per cent.

Benzosol.—A brand of guaiacol benzoate-N. N. R.

H. A. Metz Laboratories, New York, distributor. U. S. patent expired. U. S. trademark 65,165.

GUAIACOL CARBONATE.—For description see the U. S. Pharmacopeia and Useful Drugs under Guaiacolis Carbonas.

Duotal.—A brand of guaiacol carbonate-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent expired.

PROPOSOTE.—Creosote Phenylpropionate.—A condensation product of creosote and phenylpropionic acid. Proposote contains the equivalent of 50 per cent of creosote.

Actions and Uses.—Proposote is not decomposed by the gastric fluids and passes the stomach practically unabsorbed. It is decomposed in the intestines and the components are chiefly eliminated through the kidneys. The administration of proposote is claimed to be of value in bronchitis and in coughs due to bronchial infection. Animal experimentation and clinical experience tend to show that proposote causes less gastric or intestinal disturbance than creosote does.

Proposote is used for the same purposes for which creosote is administered.

Dosage.—For adults, 0.6 cc. (10 minims) three times a day. For children, 0.3 cc. (5 minims) once or twice a day. Proposote is supplied in the form of capsules only.

Manufactured by Parke, Davis and Co., Detroit. No. U. S. patent. U. S. trademark 176,953.

Proposote Capsules, 5 minims.

Proposote Capsules, 10 minims.

Proposote is prepared by treating phenylpropionic acid with creosote in the presence of phosphorus oxychloride and purification by treatment with dilute alkali solution and extraction with benzin.

Proposote is an amber colored oily liquid, having a characteristic odor resembling creosote and a slightly bitter taste. It is insoluble in water, soluble in alcohol, ether and fatty oils. The boiling point of proposote is above 360 C.; its specific gravity at 25 C. is 1.10.

Treat 5 Gm. of proposote with 4 Gm. sodium hydroxide and 20 cc. of water; heat on a steam bath until saponification is complete (1 to 2 hours), 5 cc. of alcohol being added to facilitate saponification; separate the aqueous solution and dilute it to 100 cc.; acidify with 10 per cent sulphuric acid and separate the liberated cresol. Concentrate the aqueous filtrate and allow it to cool: fine needles of hydrocinnamic acid separate.

Dissolve 1 cc. of proposote in 25 cc. of neutral alcohol and titrate with tenth-normal sodium hydroxide, using methyl red as indicator. Each cc. of alkali equals 1.5 per cent of acid calculated as phenylpropionic acid: more than 0.1 per cent is present.

Dissolve 1 cc. of proposote in 16 cc. of alcohol; transfer 1 cc. of this solution to 25 cc. of water and add 2 drops of ferric chloride solution: no brown color appears within five minutes (*limit of creosote*).

Ignite 2 cc. of proposote: the ash is not more than 0.1 per cent.

THIOCOL-ROCHE — Potassium Guaiacolsulphonate. — $C_6H_3(OH)(OCH_3)(SO_3K)$, 1:2:6.—The potassium salt of orthoguaiacolsulphonic acid, $C_6H_3(OH)(OCH_3)(SO_3H)$1:2:6.

Actions and Uses.—Thiocol-Roche acts as a sedative expectorant. It has the advantage over guaiacol in that it is comparatively tasteless, does not disturb digestion and is nontoxic. In thiocol-Roche, the guaiacol is so firmly bound that almost none is split off when the salt is administered, and it is questionable whether its action is due to small quantities of guaiacol set free or to the guaiacolsulphonic group as a whole.

It is claimed that thiocol-Roche is useful in the treatment of diseases of the respiratory tract, incipient tuberculosis and certain diarrheas.

Dosage.—From 0.3 to 1.3 Gm. (5 to 20 grains), dissolved in water or in syrup, or in the form of tablets.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffman-LaRoche, Inc., Nutley, N. J.). U. S. patent 650,218 (expired). U. S. trademark 80,717.

Syrup Thiocol-Roche: Containing thiocol-Roche 10.5 Gm., in 100 cc. (6 grains in a fluidrachm).

Thiocol-Roche Tablets, 5 grains.

Thiocol-Roche is a colorless, crystalline powder, neutral or faintly alkaline, odorless, and having a faintly bitter taste. Thiocol-Roche is soluble in water, slightly soluble in ordinary alcohol, but insoluble in absolute alcohol and in ether or oils.

If to an aqueous solution of thiocol-Roche, barium chloride solution is added, no precipitate is produced; ferric chloride produces an intense violet-blue color, which disappears on the addition of ammonia, or of concentrated solution of alkali chlorides or sulphates.

CRESOL AND CRESYLIC ACID PREPARATIONS

Cresols are phenols in which one of the hydrogen atoms has been replaced by CH_3. This substitution increases the germicidal efficiency, while the toxicity is not increased, at least not in the same ratio. The cresols, therefore, possess distinct advantages as disinfectants. In practice, they are much less toxic than phenol, because they are used more diluted, but they are far from being "nonpoisonous." Another advantage of the cresol preparations over phenol is their lower cost. Their disadvantages are the disagreeable odor, which depends mainly on impurities, their limited solubility in water, and their variable composition and activity.

They may be rendered soluble by the addition of soap, as in the official compound solution of cresol, and in several other ways. The variability is best discounted by the determination of the phenol coefficient, that is, the ratio of the germicidal power of the disinfectant to the germicidal power of phenol, tested under identical conditions. (The Council has approved the Hygienic Laboratory phenol coefficient. The details of the test are described in *Public Health Reports,* July 8, 1921, pp. 1559-1564.) A disinfectant three times as active as phenol against *B. typhosus* would have the coefficient 3 (this being about the coefficient of compound cresol solution). Most disinfectants are now sold with a statement of their coefficient. The degree of dilution for disinfection is obtained simply by multiplying by 20 the phenol coefficient; for instance, a disinfectant having the coefficient 3 would be diluted $3 \times 20 = 60$ times.

The official cresol is a mixture of the three isomers of $C_6H_4.OH.CH_3$. The "higher homologues," containing two or more methyl groups are generally referred to as cresylic acid. They have a higher disinfectant coefficient.

CRESOL.—For description see the U. S. Pharmacopeia and Useful Drugs under Cresol.

Purified Three Cresols-Mulford.—A mixture of isomeric cresols, corresponding closely to cresol, U. S. P.

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

Purified three cresols-Mulford conforms to the standards of cresol U. S. P. It also meets the following requirements: It is practically colorless. When 1 cc. is agitated with 100 cc. of water at 25 C., a clear solution results (*absence of hydrocarbons*). It distils between 195 and 205 C. When 1 cc. is mixed with 250 cc. of water and titrated with half normal sulphuric acid, using methyl orange as indicator, not more than a trace of pyridine bases is indicated. The phenol coefficient is not less than 2.5 (the value is stated on each package). The phenol toxicity, determined by the method of Hale, is not greater than 150 per cent. (the value is stated on each package).

IZAL.—An albuminous emulsion containing not less than 50 per cent of a liquid, "izal oil," which is obtained in the destructive distillation of bituminous coal, and which consists essentially of monatomic phenols boiling between 205 and 300 C. Izal is, therefore, practically free from phenol and cresols.

Actions and Uses.—Izal is a germicide and disinfectant. The germicidal efficiency of izal is claimed to be ten times as great as that of an equal quantity of phenol, but it is stated to be less toxic than phenol.

Dosage.—For general use (disinfecting, cleansing and deodorizing) a dilution of 1 in 200 is made; for mouth wash and as a gargle, douche, etc., a dilution of 1 in 250 is used. For the disinfection of urine, feces, etc., dilutions of 1 in 100 (1 fluidrachm to 1 pint of water) are advised. Izal is not intended for internal use.

Manufactured by The Abbott Laboratories, North Chicago, under license from Newton, Chambers and Company, Ltd., Thorncliffe, near Sheffield, England. No U. S. patent. U. S. trademark.

Izal oil is obtained by extraction and fractionation of substances which are obtained when certain grades of bituminous coal are distilled at controlled temperature. It is fractionated to exclude cresols.

Mix 100 cc. of izal with an equal volume of hydrochloric acid, heat to 80 C. for thirty minutes, and pour the mixture into a measuring cylinder and allow to cool: the supernatant layer of izal oil should measure at least 50 cc.

Into a standard Engler side tube flask measure 50 cc. of izal oil as obtained in the preceding test and distil through a condenser at the rate of 60 drops per minute; the thermometer bulb should be opposite the side tube, and the readings should be corrected for temperature and pressure: at least 90 per cent of the "oil" distils between 205 and 300 C.

When tested against *B. typhosus* by the U. S. Hygienic Laboratory method, izal has a phenol coefficient of 10.

KRELOS-MULFORD (DISINFECTANT).—Liquor Cresolis et Phenolis Comp.-Mulford.—A solution of cresols or higher phenol homologues and rosin soap. It is said to represent, approximately: water, 8 per cent; sodium oxide, 2 per cent; pyridin, 1 per cent; rosin acids, 15 per cent; phenols, 60 to 67 per cent, and hydrocarbons, 7 to 14 per cent.

Actions and Uses.—Krelos-Mulford (disinfectant) is an antiseptic and germicide.

It is said to be indicated whenever antiseptics or disinfectants are employed.

H. K. Mulford Company, Philadelphia, distributor. No U. S. patent or trademark.

Krelos-Mulford (disinfectant) is said to be prepared by the addition of coal tar distillates to a rosin soap solution.

It is a dark brown, almost black, liquid, having a specific gravity of about 1.040 and a characteristic cresol-like odor. With water it forms an almost white, milklike emulsion.

The bactericidal power of krelos-Mulford (disinfectant) is determined against *B. typhosus* by the Hygienic Laboratory method. The phenol coefficient, ranging from 5 to 7, is stated on the label.

PHENOCO.—A mixture of coal tar creosote and higher phenol homologues, in soap solution. It is said to contain coal tar creosote, 20 per cent, phenol homologues, 50 per cent, and soap, 30 per cent.

In the foregoing definition, the manufacturers use the term "coal tar creosote" to signify the product obtained by the destructive distillation of coal, containing 15 per cent of cresols, but no phenol; while the term "higher phenolhomologues" is used to designate phenols containing two or more methyl groups.

Actions and Uses.—Phenoco is an antiseptic and germicide, being, in the latter respect, from fifteen to sixteen times stronger than phenol against *B. typhosus* as tested by the U. S. Hygienic Laboratory method. It is stated to be noncaustic, nonirritant and, for mammals, about one-half as toxic as phenol.

It is used in minor surgery, obstetrics, gynecology, ophthalmology, otology, diseases of the skin, etc.

Dosage.—Dilutions of from 1 to 5 per cent, or higher, according to the severity of the case.

Manufactured by the West Disinfecting Co., New York. No U. S. patent. U. S. trademark 61,552.

Phenoco is said to be prepared by incorporating a nearly dry, vegetable oil soap with the coal tar creosote and phenol homologues at a temperature of 100 C. under continuous agitation until complete solution has taken place.

Phenoco is a dark brown fluid of a characteristic odor like that of coal tar. It is miscible with water in all proportions, forming a white emulsion; it is soluble in alcohol, ether, acetone and in fixed oils, forming clear solutions. It is compatible with physiologic salt solution. It is incompatible with strong alkalis and acids. When tested against *B. typhosus* by the "phenol coefficient" method of the Hygienic Laboratory of the U. S. Public Health Service, it is said to be from fifteen to sixteen times stronger, as a germicide, than pure phenol.

The chemical composition of phenoco is controlled according to the method published in Bulletin 107, Bureau of Animal Industry, "The Analysis of Coal-Tar Creosote and Cresylic Acid Sheep Dips."

CRESOL DERIVATIVES

The toxicity and local actions of the cresols, as of other phenols, may be diminished by "masking" the active OH group through replacement of the H by acid radicals.

CRESATIN-Dr. N. Sulzberger.—*m*-Cresyl Acetate.—$CH_3C_6H_4.O(CH_3CO)$.—The acetic acid ester of metacresol, $CH_3C_6H_4.OH$.

Actions and Uses.—Cresatin-Dr. N. Sulzberger is said to possess antiseptic and analgesic properties, and is apparently free from toxic effects. It is said to be useful in the treatment of affections of the nose, throat and ear, such as follicular tonsillitis, nasal suppuration due to ethmoid diseases, atrophic nasopharyngeal catarrhs, furunculosis of the external auditory canal and purulent otitis media. When applied to mucous membranes it is said to cause no irritation, sloughing or discomfort.

Dosage. — Cresatin-Dr. N. Sulzberger may be employed either in the pure form, or in dilution with oils or alcohol by direct application or spray.

Manufactured by Sharp & Dohme, Baltimore. U. S. patent 1,031,971 (July 9, 1912; expires July, 1929). U. S. trademark 80,533.

The chemical properties of meta-cresyl acetate were studied by C. Panoff in 1903 (*Jour. Russ. Phys. Chem. Ges.* **35**: 93, 1903).

Cresatin-Dr. N. Sulzberger occurs as a colorless, oily liquid, possessing a characteristic odor. It is practically insoluble in water, but soluble in the ordinary organic solvents, miscible with liquid petrolatum, fixed and volatile oils and is volatile with steam.

If 10 cc. of cresatin-Dr. N. Sulzberger is shaken for one minute with 100 cc. of water and filtered through a wet filter, the filtrate has a neutral reaction, and does not produce a violet color with ferric chloride solution, or a turbidity with silver nitrate solution. If 10 cc. of cresatin is evaporated it leaves after incineration no weighable residue.

CRYOGENINE.—Phenylsemicarbazide.—$C_6H_5.NH.NH.CO.NH_2$.

Actions and Uses.—Cryogenine is an antipyretic and analgesic. It is claimed that cryogenine does not affect digestion and that it has scarcely any effect on the circulation and respiration. After administration of cryogenine, the urine is highly colored, but it is claimed to be without deleterious action on the kidney.

Cryogenine is claimed to be useful as an antipyretic in febrile conditions As an analgesic, it is said to be of value in rheumatism, headache, sciatica, gout and in painful conditions generally.

Dosage.—As an antipyretic, 0.25 to 2 Gm. (4 to 30 grains) per day. As an analgesic, from 1 to 3 Gm. (15 to 45 grains) per day.

Manufactured by Laboratories A. Lumiere, Lyons, France (Gallia Laboratories, Inc., New York, distributor). No U. S. patent. U. S. trademark 67,918.

Cryogenine Tablets 0.5 Gm.

Cryogenine is a white crystalline powder; odorless; taste slightly bitter. It is soluble in about 100 parts of water at 20 C.; soluble in ether, acetone, chloroform and benzene. It melts at 172 C.

Cryogenine reduces potassium permanganate solution with precipitation of manganese dioxide; it also reduces iodates in alkaline solution, potassium bichromate and alkaline cupric tartrate solution. Add a few drops of alkaline cupric tartrate solution to 5 cc. of a saturated aqueous solution of cryogenine: a green coloration results. On heating, a red precipitate results.

CYPRESS OIL.—Oleum Cupressi.—An oil distilled from the leaves and young branches of *Cupressus sempervirens.*

Actions and Uses.—Cypress oil is said to be useful when administered by inhalation for the relief of whooping-cough.

Dosage.—The oil should be diluted with 5 parts of alcohol and 15 cc. (4 fluidrachms) of the mixture should be sprinkled three or four times daily over the coverlet, pillow and underwear of the child. The application may be repeated once or twice during the night, if recurring attacks are unusually severe.

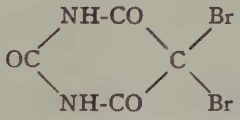
Cypress oil is a yellowish liquid with a pleasant odor suggesting cypress. After evaporation, it leaves an odor that reminds one of laudanum or amber. Its specific gravity is from 0.88 to 0.89 at 15 C. and its optical rotation is + 4 to + 18. The oil is soluble in from 3 to 6 parts of 90 per cent alcohol.

Cypress oil consists chiefly of furfural, d-pinene, d-camphene, cymene, d-sylvestrene, d-terpineal and esters of the same, l-cadinene and cypress camphor.

Oil of Cypress-Schimmel and Co.—A brand of cypress oil-N. N. R.

Manufactured by Schimmel & Co., Miltitz, near Leipzig, Germany (Fritzsche Bros., Inc., New York, distributor). No U. S. patent or trademark.

DIBROMIN.—Dibromobarbituric Acid.—Dibromomalonylureide.



Actions and Uses.—Dibromin is an antiseptic and germicide proposed for use in solution as in irrigating fluid and wet dressings for flushing cavities, irrigating infected wounds and for saturating gauze packing. Dibromin is claimed to be practically free from irritating or toxic properties in the concentrations required for therapeutic use.

Dosage.—To determine the strength of dibromin solutions which may be safely used on an individual without producing irritation, it is advised to begin with solutions of 1 in 10,000 (6 grains to one gallon) and then to gradually increase the concentration.

Manufactured by Parke, Davis & Co., Detroit. U. S. patent applied for. U. S. trademark 158,277.

Dibromin Capsules, 6 grains.

Dibromin occurs as a crystalline, colorless powder; almost odorless; taste slightly astringent. It melts with decomposition at about 150 C. One part of dibromin dissolves in about 33 parts of water; soluble in ether, glycerin and alcohol; insoluble in fixed oils. The dry salt is permanent, but aqueous solutions decompose slowly. It is decomposed by alkalis, reducing agents and most organic substances.

Heat about 0.25 Gm. of dibromin to 160 C.: bromine is evolved. Heat about 0.25 Gm. dibromin with an aqueous solution of sodium carbonate: the odor of bromoform develops.

Dissolve about 0.1 Gm. of dibromin, accurately weighed, in about 20 cc. of water, add 20 cc. potassium iodide solution and an excess of diluted sulphuric acid. After one minute determine the liberated iodine by titration with tenth normal sodium thiosulphate: iodine liberated corresponds to not less than 54.8 per cent of bromine: this corresponds to not less than 98 per cent of dibromobarbituric acid.

DIGESTIVE ENZYMES

As a result of the replies to a questionnaire sent to the members of the American Gastro-Enterological Association, W. A. Bastedo reported (Jour. A. M. A., Sept. 5, 1925) that many members of the association do not prescribe digestive enzymes, while those who do employ such enzymes confine their use almost wholly to cases of demonstrated or believed enzyme deficiency; almost all who prescribe them show no great enthusiasm over the results of their use, except possibly in the case of pancreatin in proved pancreatic deficiency.

In consideration of the replies to the questionnaire, and in consideration of the fact that no favorable evidence has since become available, all digestive enzyme preparations have been omitted save those recommended for use outside the body for the digestion of food previous to administration and locally for the softening of dead tissues or the solution of false membranes.

Proteolytic Enzymes

PEPSIN GROUP, INCLUDING RENNIN

ENZYMOL.—An extract prepared from the fresh animal stomach, said to contain the activated gastric enzyme in association with the soluble constituents with which the proenzyme is naturally associated. It is free from alcohol, contains a trace of thymol, and has an acidity due to combined hydrochloric acid equivalent to 0.26 to 0.3 per cent of actual hydrochloric acid. It is adjusted to a definite proteolytic power by the U. S. P. assay method for pepsin, and contains 25 per cent of glycerin by weight.

Actions and Uses.—Enzymol is said to be useful as an application to old sores, ulcers and slow-healing wounds. It is said to correct offensive odors, to exert a solvent action on pus and sloughing and necrotic tissue, and to impart a healing stimulus. It is said to have been effective in cases which have long remained unhealed and have resisted treatment.

Dosage.—Enzymol is made ready for use by the addition of from one-half to one or two volumes of water; for the solution of necrotic and carious bone, and in some large abscess cavities, it is advised that the preparation be diluted with two volumes of 0.2 per cent solution of hydrochloric acid. A small vial, containing diluted hydrochloric acid and a pipette for measuring, accompany the package of enzymol.

Manufactured by Fairchild Bros. and Foster, New York. No U. S. patent. U. S. trademark 44,769.

Enzymol is a light straw-colored fluid.

The presence of the various groups of proteins is shown by the following reactions: On heating to boiling, the fluid gives a copious coagulation. The filtrate from this gives a marked precipitate with phosphotungstic acid. The protein derivatives remaining in solution may be determined by silver nitrate and barium oxide according to Hall. Alcohol in excess, likewise, gives a copious precipitate. The proteolytic power for pepsin when acidified and tested by the method of the U. S. P. should be such that 4 cc. will dissolve 800 Gm. of coagulated egg albumin in two and one-half hours.

TRYPSIN GROUP

TRYPSIN.—The proteolytic enzyme of the pancreas, separated to a considerable extent from the other constituents of the gland.

Actions and Uses. — See discussion of tryptic enzymes in preceding article, Digestive Enzymes.

Trypsin-Armour.—It is stated that trypsin-Armour is standardized so that 1 part digests at least 100 parts of casein according to the Fuld-Gross method.

Dosage.—Trypsin-Armour is applied locally by means of a brush or as a spray. About 0.4 Gm. (6 grains) is mixed with 0.125 Gm. (2 grains) sodium bicarbonate and triturated in a mortar while 1 or 2 drachms of distilled water is added. The mixture is then warmed to from 38 to 40.6 C. and applied immediately. The application may be repeated several times an hour if necessary, a fresh solution being made before each application. The internal dose is 0.125 Gm. (2 grains), or more, three times daily. It should not be used for hypodermic injection.

Manfactured by Armour & Company, Chicago. No U. S. patent or trademark.

Trypsin-Armour is prepared from the fresh pancreas of hogs with the view of retaining the proteolytic ferment in an especially active condition. It has been activated by enterokinase.

It is a light yellow powder, possessing a faint odor and a meatlike taste. It is not completely soluble in water at once, but dissolves almost entirely in time.

Trypsin-Fairchild.—When tested by the Fuld-Gross method it is said that trypsin-Fairchild converts 200 times its weight of casein to the standard end-point.

Dosage.—Trypsin-Fairchild may be given in doses of 1 grain (equal to from 4 to 5 grains pancreatin-U. S. P.) and upward, best in a capsule with some diluent, as milk sugar and if indicated, with sodium bicarbonate. It is locally applied in solution or after trituration of the trypsin with some appropriate diffusible powder.

Manufactured by Fairchild Brothers and Foster, New York. No U. S. patent or trademark.

Trypsin-Fairchild, is a fine dry powder, in which form the enzyme is permanent when protected from moisture. It is slowly but not completely soluble in water.

Trypsin-Fairchild, has from four to five times the strength of pancreatin-U. S. P. The tryptic power of Fairchild's trypsin by the method proposed by Sir William Roberts is 10,000 units.

DIGITALIS PRINCIPLES AND PREPARATIONS

The digitalis group embraces many crude drugs and proximate principles which have a peculiar action on cardiac muscle. Digitalis and strophanthus have been investigated far more than the others, and we are much better informed concerning their actions; from them are derived the active principles and proprietary preparations which have been included in N. N. R.

Cardiac Action.—The cardiac action of the individual drugs of the group is similar and the claims made for the different preparations concern the removal of the disadvantages that have been experienced in the use of the drugs belonging to the digitalis group. The first disadvantage of digitalis medication is the varying strength of the crude drugs. This uncertainty can be avoided by the use of the isolated, definite principles, or to a considerable extent by the use of physiologically standardized preparations. The pharmacopeia requires that digitalis, squill, and strophanthus be standardized against crystallized ouabain by the one-hour frog method in which the ventricle of the frog's heart is caused to stop in systole in one hour after the injection of the drug into the lymph sac. The following methods of standardization are also used extensively:

1. The frog-lethal dose method (M. L. D. in twelve or twenty-four hours).
2. The guinea-pig lethal dose method.
3. The intravenous cat method.

Differences in Emetic Action.—The digitalis principles are irritant to certain mucous membranes and the subcutaneous tissues and it has been deduced that the nausea and vomiting which sometimes follow the oral administration of these drugs result from irritation of the gastro-intestinal tract. These symptoms might be avoided by the hypodermic or intravenous use of these drugs or by the use of certain preparations. It has been shown, however, that digitalis does not markedly irritate the stomach or intestines directly, but that its preparations cause nausea and vomiting almost entirely through their action on the heart itself. Digitonin and similar substances are present in digitalis in amounts far too small to cause gastric disturbances. It has been shown also that the emetic action is roughly proportional to the cardiac effects of the various members of the group, and when this undesired action is induced it cannot as a rule be avoided by changing the mode of administration, or by resorting to other members of the group.

Differences in Absorption.—Digitalis and preparations representing the entire drug and also digitoxin are absorbed fairly readily from the alimentary tract, and hence their actions may be limited to the therapeutic stage, whereas strophanthus and strophanthin are absorbed more slowly and irregularly with correspondingly greater difficulty in limiting their actions to those desired, when they are administered by the mouth. This disadvantage has been overcome by administering strophanthin intramuscularly or intravenously, in much smaller doses, however.

Differences in Cumulative Action.—The effects of all the digitalis bodies are said to be cumulative. This cumulative effect is especially pronounced in the case of digitalis itself and digitoxin. It is much less pronounced in the case of strophanthus, strophanthin and true digitalin.

Digitalis Principles

The disadvantages of all the drugs of the digitalis group have served as a constant stimulus in the search for pure principles suitable for subcutaneous and intravenous administration; but despite the numerous investigations directed toward this end, the chemistry of digitalis and other members of the group is very imperfectly understood. Several digitalis principles have been isolated in a greater or less degree of purity. Of these, digitoxin and digitalin together represent very nearly the crude drug digitalis. The digitalin on the market, however, is not the true digitalin, but the different brands consist of mixtures of two or more principles.

It must be remembered, therefore, that Merck's "crystallized" digitalin, Merck's "pure" digitalin and the "true" digitalin of Boehringer and Soehne, which naturally might be supposed to be identical, differ somewhat in their action.

Proprietary Digitalis Preparations.—Several digitalis preparations have been introduced into therapeutic use with the claim that they are composed either of pure principles, or of purified extracts of digitalis, and that they are devoid of certain disadvantages possessed by the preparations of the U. S. Pharmacopeia.

It may be said at once that there is no proof that any of these proprietary preparations can be used to greater advantage than digitalis and its galenicals in the majority of cases of cardiac disease. The Council, therefore, especially urges on clinicians the necessity of acquiring skill in the use of the digitalis principles by the careful observation of the actions of a very few of the members of the group, rather than trying to use without discrimination, the large number of preparations which are offered. The following principles obtained from the digitalis group are described in New and Nonofficial Remedies: digitalein, crude; digitalin, true; digitalin, "French"; digitalin, "German"; digitoxin; ouabain crystallized, and cymarin.

DIGALEN-ROCHE (CLOETTA).—A sterile solution containing in each cubic centimeter 0.3 mg. of an active derivative of digitalis as isolated by Cloetta, containing 7.5 per cent of alcohol.

Actions and Uses.—The same as those of digitalis. After a time under conditions which have not yet been determined satisfactorily, digalen-Roche (Cloetta) sometimes deteriorates, even when the container remains unopened. Experiments made under the direction of the Council show that the preparation has varied both quantitatively and qualitatively in its action.

Dosage.—The average dose is from 1 to 2 cc. (15 to 30 minims). The maximum daily dosage is 6 cc. (90 minims). Digalen-Roche (Cloetta) is also suitable for intramuscular and intravenous injection. Intravenous injections of 1 cc. (15 minims) may be repeated at intervals of one-half to one hour as necessary.

Manufactured by Hoffmann-LaRoche, Inc., Nutley, N. J. No U. S. patent. U. S. trademarks 43,593; 83,738.

Ampules Digalen-Roche (Cloetta), 1.1 cc.

Tablets Digalen-Roche (Cloetta): equivalent to digalen-Roche (Cloetta) 0.5 cc.

Hypodermic Tablets Digalen-Roche (Cloetta): equivalent to digalen-Roche (Cloetta) 1 cc.

Digalen-Roche (Cloetta) is prepared as follows:

The dried and finely powdered leaves of digitalis are extracted with diluted alcohol; then the extract is mixed with lead acetate solution in order to remove chlorophyll and resins, and filtered. From this filtrate the excess of lead is precipitated with sodium sulphate and the alcohol distilled off *in vacuo*. From the remaining aqueous solution, the active derivative of digitalis contained in digalen-Roche (Cloetta) is extracted by ethereal solvents and precipitated afterward in an amorphous and pure condition according to a special secret method. Each cc. of digalen-Roche (Cloetta) contains the active derivative of digitalis 0.3 mg. in a menstruum consisting of glycerin 1,000 parts, distilled water 1,600 parts and alcohol 7.5 per cent, making an isotonic sterile solution.

Digalen-Roche (Cloetta) is a colorless or slightly yellowish liquid of an agreeable aromatic odor with a sweet taste which subsequently becomes bitter.

The active derivative contained in digalen-Roche (Cloetta) is an amorphous, white or slightly yellow powder. It is stated to have a solubility five times as great as that of crystallized digitoxin. It is stated to dissolve readily in alcohol and chloroform, and less readily in ether. It has an intensely bitter taste and causes violent sneezing.

To 2 cc. of digalen-Roche (Cloetta) add a few drops of diluted acetic acid and extract with chloroform. Evaporate the chloroform extract and dissolve the residue in about 2 cc. of glacial acetic acid containing a trace of ferric chloride. To this solution add strong sulphuric acid without mixing so as to form a separate layer: a brown ring forms between the two layers which becomes broader after some hours and expands toward the top in a blue-green to black shade, and toward the bottom in a reddish-brown one. The acetic acid finally acquires a dark green-blue color.

DIGIFOLINE-CIBA.—A digitalis preparation containing the active glucosides of digitalis, free from extractive matter. It is standardized to have the strength of digitalis leaves as standardized by the frog method of Focke ("Nachweis und Bestimmung von Giften auf biologischem Wege," by H. Fuhner, 1911).

Actions and Uses.—The same as those of digitalis.

Dosage.—Digifoline-Ciba may be administered orally, rectally, or by subcutaneous, intramuscular or intravenous injection: three digifoline-Ciba tablets by mouth or 2 cc. of digifoline-Ciba solution hypodermically, daily, during three days, followed by intervals of ten days, if it is necessary to repeat the treatment;

in acute conditions, four digifoline-Ciba tablets orally or 3 cc. of digifoline-Ciba solution hypodermically or 1 to 2 cc. of digifoline-Ciba solution intravenously. The maintenance dose is one digifoline tablet daily for five days in every fourteen. The massive dose method with digifoline-Ciba is as follows: The average dose required having been determined on the basis of 1 minim of digifoline-Ciba solution for each pound of body weight, one fourth of this is given at once and the remainder is divided in from three to six doses and administered at intervals of four to six hours until the desired effect is obtained or some effect of digitalization becomes manifest.

Manufactured by the Society of Chemical Industry in Basle, Basle, Switzerland (Ciba Company, Inc., New York, distributor). No U. S. patent. U. S. trademark 99,808.

Ampules Digifoline-Ciba Solution, 1 cc.: Each ampule contains 1.1 cc. of a digifoline-Ciba solution, each cubic centimeter containing digifoline-Ciba equivalent to 0.1 Gm. (1½ grains) of digitalis leaves standardized by the Focke method.

Ampules Digifoline-Ciba Solution, 5 cc.: Each ampule contains 5 cc. of a digifoline-Ciba solution, each cubic centimeter containing digifoline-Ciba equivalent to 0.1 Gm. (1½ grains) of digitalis leaves standardized by the Focke method.

Digifoline-Ciba Liquid: Each cubic centimeter contains digifoline-Ciba equivalent to 0.1 Gm. (1½ grains) of digitalis leaves standardized by the Focke method. It contains 12 per cent of alcohol.

Tablets Digifoline-Ciba: Each tablet contains digifoline-Ciba equivalent to 0.1 Gm. (1½ grains) of digitalis leaves standardized by the Focke method.

Dried and finely ground digitalis leaves are extracted with distilled water. The neutralized filtrate is then treated with alcohol, precipitated with a solution of lead acetate and filtered. The filtrate, after the removal of the lead and neutralization, is filtered and concentrated to a certain volume in a high vacuum at a temperature not exceeding 30 C. The active principle which separates through the foregoing concentration is collected and dried under a high vacuum at a temperature of 40 C. It is then dissolved in methyl alcohol, the filtrate treated with chloroform and the chloroform, separated from the aqueous solution, distilled off and the residue dissolved in methyl alcohol. The aqueous solution which has been separated from the chloroform solution is treated with a mixture of ether two parts and benzene one part; the ether-benzene extract is concentrated under high vacuum at low temperature and the remaining residue dissolved in methyl alcohol. The several methyl alcohol solutions are mixed, decolorized with charcoal and concentrated under a high vacuum to a dry residue, which constitutes digifoline-Ciba.

Digifoline-Ciba is almost colorless and odorless, with a slightly bitter taste. It is an amorphous brownish powder, soluble in water, methyl alcohol and ethyl alcohol; insoluble in ether and petroleum ether.

Prepare two solutions: (A) Dissolve ferric sulphate, 5 Gm., in water, 100 cc., filter and add 5 cc. of the filtrate to 500 cc. of pure glacial acetic acid; (B) add 5 cc. ferric sulphate solution (ferric sulphate, 5 Gm. in water, 100 cc.) to 500 cc. pure sulphuric acid. Dissolve a trace of digifoline-Ciba in 5 cc. of solution A and layer this solution carefully on 5 cc. of solution B: at the point of contact, a dark band appears; the lower layer assumes a red color and the upper layer a bluish-green color; on standing, the bluish-green layer turns to indigo-blue.

DIGITALEIN, CRUDE.—Digitaleinum Crudum.—A mixture of glucosides from *Digitalis purpurea* prepared according to the process of Schmiedeberg. Its composition is variable, but it probably contains digitoxin and digitalein.

Actions and Uses.—Digitalein acts similarly to digitalis on the heart.

Its uses are the same as those of digitalis.

Dosage.—From 0.001 to 0.002 Gm. (1/60 to 1/30 grain), two or three times a day.

Commercial digitalein is an amorphous, yellowish-white, bitter powder, soluble in water and absolute alcohol, insoluble in chloroform and ether. The aqueous solution foams on shaking. The solution yields a precipitate on the addition of lead acetate, ammonia water or tannic acid.

DIGITALIN, TRUE.—Digitalinum Verum Kiliani.—Schmiedeberg's Digitalin—$C_{35}H_{56}O_{14}$.—A glucoside found in the seeds and leaves of *Digitalis purpurea* and derived commercially from "German" digitalin.

Actions and Uses.—The same as those of digitalis. Its action is not so persistent as that of digitoxin. True digitalin is more actively emetic than the other digitalis bodies in proportion to its cardiac activity, and it probably has no advantages over the better known members of the group.

Dosage.—It is impossible at present to state the correct dose for digitalinum verum Kiliani. Some authorities have given the same dose as that for digitoxin, whereas others correctly give it as much larger. At least, it is quite certain that digitalin is not so active as digitoxin. It is best given in pills made by trituration with sugar of milk and massing with glucose. Aqueous solutions of digitalin rapidly lose their strength and should be freshly prepared.

To a solution of 1 part "German" digitalin in 4 parts of 95 per cent alcohol, 5 parts of ether by weight (specific gravity 0.720) are added and the mixture allowed to stand in a closed vessel for twenty-four hours. In the clear supernatant solution, the quantity of dissolved substance is estimated and the whole then subjected to a vacuum distillation until its weight becomes 1.6 times that of the total dissolved substance. To this concentrated solution, water, in an amount 2.4 times the weight of dissolved substance, is added, forming a solution containing approximately 20 per cent alcohol, from which crude digitalin gradually separates on standing. The crude product is washed first with 10 per cent alcohol and then with water, and finally dried at a moderate temperature. Further purification is effected by boiling the alcoholic solution with animal charcoal (Kiliani's method in Hager, H.: Handbuch der pharmaceutischen Praxis, Berlin, B. Fischer and C. Harturch **1**: 1030, 1903).

Digitalin occurs as a white amorphous powder, or in characteristic, granular masses. It melts at 217 C. and becomes yellow. It is soluble in 1,000 parts of water and in 100 parts of 50 per cent alcohol, but nearly insoluble in ether and chloroform. Digitalin dissolved in alcohol, and treated with very dilute acid and heat yields digitaligenin and two sugars.

With concentrated sulphuric acid, digitalin forms a golden yellow solution which on the addition of potassium hypobromite solution changes to a magnificent rose red or violet red. If a little digitalin is dissolved in from 3 to 4 cc. of glacial acetic acid to which a trace of ferric chloride solution has been added and the mixture carefully underlaid with concentrated sulphuric acid (Keller's reaction) a deep carmine-red band appears. The lower layer of the acetic acid is light yellow, changing to brownish (*distinction from digitoxin*). Sulphuric acid containing a little ferric sulphate gives, with a little digitalin, at first an intense golden yellow color, and then a red solution; this color rapidly changes to a beautiful and permanent violet. If too much digitalin is used, the red remains and only the surface layer becomes violet. When heated on platinum foil, digitalin should burn without leaving a weighable residue. If a granule of digitalin is covered with 2 cc. of 10 per cent potassium hydroxide solution, no color should develop within one minute (*absence of other glucosides*).

If digitalin is stirred to a thin paste with water, and for every 100 parts of water used, 22 parts of amyl alcohol is added, with shaking, and the mixture set aside in a closed vessel for twenty-four hours, the presence of digitonin will be indicated by the formation of distinct masses of crystals.

DIGITALIN, "FRENCH."—Homolle's Digitalin.—Digitaline Amorphe.—Digitaline Chloroformique.—A mixture obtained from *Digitalis purpurea* by the method of Homolle, consisting mainly of digitalinum verum Kiliani.

Actions and Uses.—Its action is like that of digitoxin. Its uses are the same as those of digitalis.

Dosage.—What has been said with regard to the dose of digitalinum verum applies to the "French" digitalin; the dose is variously given as from 0.00025 to 0.002 Gm. (1/240 to 1/30 grain). The maximum daily dose is 0.006 Gm. (1/10 grain). It must be used with caution and its action carefully watched.

One hundred grams of powdered digitalis leaves are moistened with 1 liter of water and slowly exhausted in a percolator until the percolate amounts to 3 liters. This is precipitated with 250 Gm. of lead acetate and the filtrate from the precipitate is treated with 40 Gm. of crystallized sodium carbonate and 20 Gm. of sodium ammonium phosphate, in order to remove the excess of lead. The filtrate is precipitated with 40 Gm. of tannic acid. The tannate is mixed with 25 Gm. of powdered litharge and 50 Gm. of purified animal charcoal and dried. From the dried mass the digitalis bodies are extracted with 90 per cent alcohol, the latter is distilled off and the residue washed with distilled water and again taken up in 90 per cent alcohol. This is again distilled and the residue exhausted with chloroform. When the latter is expelled the digitalin remains behind (Hager: Handbuch der pharmaceutischen Praxis, **1**: 1035, 1903).

"French" digitalin is a yellowish-white, amorphous powder of a peculiar aromatic odor and little taste. It is neutral to litmus, almost insoluble in water, soluble in alcohol and chloroform and insoluble in ether. It softens at 90 C. and begins to melt at 100 C. It is not precipitated by solutions of lead salts, but with tannic acid it forms a tannate insoluble in water. Concentrated sulphuric acid dissolves digitalin "French," producing a yellow color, which finally changes to an emerald-green.

DIGITALIN, "GERMAN."—Digitalinum Germanicum.—A mixture of glucosides obtained from digitalis seeds according to the process of Walz, and consisting largely of digitonin, with digitalin verum and other glucosides.

Note.—Digitonin is given as a synonym for crystallized digitalin by some manufacturers; and it is to be observed particularly that this is quite different from "true digitalin" or the "crystalline digitaline" of the French Pharmacopeia.

Actions and Uses.—These are similar to those of digitalis.

Dosage.—What has been said of the uncertainty of dosage of true digitalin must obviously apply with even greater force to "German" digitalin, since the activity of the latter probably depends mainly on the true digitalin that it contains. The dose of "German" digitalin was formerly given as 0.001 to 0.002 Gm. (1/60 to 1/30 grain), maximum dose 0.004 Gm. (1/15 grain), with a maximum per day of 0.02 Gm. (1/3 grain). Many clinicians, however, have used very much larger doses without ill effects, and the relative activity of certain specimens of the "German" digitalin and other members of the group would seem to indicate that such specimens of "German" digitalin might be given safely in daily doses of a grain, or possibly more.

As "German" digitalin (so-called digitalinum purum) is a mixture of very powerful active principles, the proportion of which may vary with changes in the manipulations, it is important that the directions for its preparation should be carefully followed, and caution should be exercised to purchase only such products as the manufacturers can guarantee to have been made with the necessary care.

Digitalis seeds are extracted with alcohol, the alcohol driven off, the extract diluted with water and purified by precipitation with lead acetate. The filtrate is freed from lead by sodium phosphate. From the liquid thus purified, the digitalis bodies are precipitated with tannic acid, the tannate well washed with water and decomposed with lead or zinc acetate. The digitalis thus separated is taken up in alcohol, the latter carefully distilled off and the residue washed with ether as long as it takes up anything. The digitalin purified in this way is dried at a low temperature and finally powdered. (Hager: Handbuch der pharmaceutischen Praxis **1**: 1032, 1903).

"German" digitalin is a yellowish-white, amorphous powder, soluble in water and alcohol, insoluble in ether and chloroform. It is said to contain from about 50 to 60 per cent of digitonin and from 5 to 6 per cent of digitalinum verum, the remainder being other glucosides.

Sulphuric acid containing a trace of ferric sulphate produces with digitalin, "German," an intense golden-yellow coloration, changing to red and finally to a permanent reddish-violet.

DIGITOS.—A preparation of water soluble active principles of digitalis leaves, containing not more than 6 per cent of alcohol. It is standardized by determining the lethal dose for guinea-pigs so that 1 cc. is fatal to a 250 Gm. animal.

Actions and Uses.—The same as those of other digitalis preparations. Digitos is suited for intramuscular and intravenous administration, but is not adapted for oral administration, because the water-soluble principles of digitalis are not always well absorbed from the digestive tract. A marked effect on the pulse and heart has been observed within one-half hour after the administration of digitos.

Dosage.—The same as that of tincture of digitalis. It may be given intramuscularly or intravenously in doses of from 0.3 to 4 cc. (5 to 60 minims) at intervals of a day or more.

Manufactured by H. K. Mulford Co., Philadelphia. No U. S. patent. U. S. trademark 208,314.

Digitos Ampules, 1 cc.

Digitos Ampules, 5 cc.

Digitos is prepared from dried digitalis leaves. These are extracted with chloroform; the dried marc is extracted with a mixture of ether and alcohol, rendered alkaline with ammonia; this extract is shaken with water and the ethereal layer is evaporated at a low temperature until the ether is removed; water is added and the evaporation continued in vacuo until the alcohol is reduced to about 6 per cent. The residual liquid is adjusted to a definite pH range and sterilized by candle filtration.

Digitos is a yellow, transparent or slightly opalescent liquid, free from tannin and contains not more than 0.5 per cent of solids.

DIGITOXIN.—Digitoxinum.—Digitaline Cristallisée (Nativelle).—$C_{34}H_{54}O_{11}$.—A glucoside occurring in the leaves of *Digitalis purpurea.* It is the chief active principle of digitalis.

Actions and Uses.—Digitoxin acts much like digitalis.

The cardiac action of digitoxin is persistent, and when the therapeutic effects have passed off, a smaller amount will be required as a rule to reinstate the desired effects than was needed in the first instance. Locally, it is extremely irritant; hence it cannot be used for subcutaneous or intramuscular injection. Penzoldt asserted that gastric irritation might be avoided by giving the drug only on a full stomach; but since it has been shown that the nausea and vomiting are almost altogether, if not wholly, of cardiac origin, it is difficult to understand how the condition of the stomach contents would influence these disturbances except through a delayed absorption.

Dosage.—The toxicity of digitoxin, though very great, has been exaggerated, probably owing to the appearance of symptoms after too frequent repetition of the dose, and the single dose has been given as 0.00025 Gm. ($\frac{1}{240}$ grain), and a maximum daily dose of 0.001 Gm. ($\frac{1}{60}$ grain). These doses are undoubtedly too small when it is desired to induce the therapeutic action promptly, though they are approximately accurate when the dosage is to be continued for a time after the therapeutic effects are induced. A sharp distinction should, therefore, be made between the single or daily dose for *continued use* after the desired effects have been induced, and the dose required at the beginning of treatment.

The beginning single dose is 0.0005 Gm. ($\frac{1}{120}$ grain), and the maximum beginning daily dose is 0.001 Gm. ($\frac{1}{60}$ grain). The dose must be reduced, or stopped, immediately when the therapeutic effect or toxic symptoms are induced.

Antidotes: Emetics, tannin, nitroglycerin, morphin, alcoholic stimulants or camphor.

Digitoxin occurs in thin, colorless, rectangular, anhydrous leaflets, odorless and having a bitter taste. It is slightly soluble in water, ether and amylic alcohol; easily soluble in alcohol and in chloroform; insoluble in benzin or carbon disulphide; slightly soluble in fatty oils. Digitoxin should not melt below 240 C. If a fragment of digitoxin is dissolved in 2 cc. of glacial acetic acid containing a trace of ferric chloride and the solution poured on 2 cc. of concentrated sulphuric acid, a brown color should be produced at the zone of contact of the two liquids. This color gradually changes to green and finally to indigo blue; after half an hour the entire acetic-acid layer will become blue. Digitoxin dissolves in cold, concentrated, hydrochloric acid to a colorless solution, but if this solution be heated on the water bath for some time a green color should be obtained.

If dried at 100 C., digitoxin should not lose more than 1 per cent of its weight (limit of *adhering moisture*).

Digitoxin-Merck.—A brand of digitoxin-N. N. R.
Merck & Co., Inc., Rahway, N. J., distributor.

Related Digitalis Principles

CYMARIN.—A neutral, nonglucosidal substance obtained from *Apocynum cannabinum* or *Apocynum androsemifolium*.

Actions and Uses.—Experiments on animals show that cymarin is about equal in activity to the official amorphous strophanthin, which it resembles closely in many of its pharmacologic actions, being far more active after intravenous or intramuscular injection than after oral administration. Toxic doses cause emesis probably through the action on the heart.

Its uses are much like those of digitalis, but it is not absorbed so readily from the gastro-intestinal tract, at least in animals, and probably in man; hence it is better suited for those cases in which intramuscular or intravenous injection is required to elicit the action promptly. (The usual precautions are necessary.)

Dosage.—Single dose for *oral administration* 0.0003 Gm. (1/200 grain); daily 0.001 to 0.002 Gm. (1/60 to 1/30 grain). Single or daily dose by intravenous or intramuscular injection, 0.0005 to 0.001 Gm. (1/120 to 1/60 grain). Cymarin is sold only in the form of Tablets Cymarin and Ampules Cymarin Solution, described below.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (Winthrop Chemical Co., Inc., New York). U. S. patent 1,113,714 (Oct. 13, 1914; expires 1931). German patent 255,537. U. S. trademark 96,390.

Ampules Cymarin Solution: representing 0.001 Gm. (1/60 grain) of cymarin.

Tablets Cymarin: cymarin 0.3 mg. (1/200 grain).

Cymarin was described by Taub and Fickewirth (*Arch. f. d. ges. Physiol.* **153**: 239), and according to the German patent (255,537) is prepared by extracting *Apocynum cannabinum* and *Apocynum androsemifolium* with organic solvents at a low temperature to prevent decomposition of the active substance, and subsequent recrystallization.

Cymarin occurs as colorless, thick, prismatic crystals possessing a bitter taste. It is only slightly soluble in cold water, more soluble in hot water. It is with difficulty soluble in benzene, ether and carbon disulphide, but dissolves easily in acetone, alcohol and chloroform. When heated it begins to soften at 130 C. and becomes completely liquid at from 135 to 140 C. Cymarin is very sensitive even to weak organic acids, although it is not a glucoside.

If cymarin is dissolved in hydrochloric acid, a colorless solution results which on standing becomes green and on heating becomes turbid and then yields a resinous precipitate. If cymarin is dissolved in concentrated sulphuric acid, a brown solution results. If a trace of cymarin is dissolved in 2 cc. of glacial acetic acid, to which is added 3 drops of a 1 in 20 solution of potassium dichromate, a solution will be formed which, when poured on an equal volume of concentrated sulphuric acid, will exhibit at first a brown zone and above that a bright green layer. If a trace of cymarin is dissolved in 2 cc. of glacial acetic acid, to which is added a drop of concentrated ferric chloride solution, a solution will result which, when poured on an equal volume of concentrated sulphuric acid, will develop a dark zone, and then a bluish green line, which gradually colors the acetic acid a deep blue. If a trace of cymarin is dissolved in 10 cc. of water and

5 cc. of normal sodium hydroxide solution, a solution will result which, when diluted with 1 or 2 drops of a hydrochloric acid solution of diazobenzene chloride or sodium nitrite, yields a blue violet color, which on acidifying changes to a brick red. If a trace of cymarin is dissolved in 2 cc. of glacial acetic acid containing a drop of bromine, a solution will be formed which, after being warmed on the water bath a few minutes, yields a precipitate of white flakes on the addition of double the volume of distilled water.

OUABAIN, CRYSTALLIZED.—Ouabainum.—Crystallized Strophanthin.—G-Strophanthin Thoms.—$C_{30}H_{46}O_{12} + 9H_2O$.—A glucoside, obtained from *Acokanthera ouabaio* by Arnaud, or, as now commonly prepared, from *Strophanthus gratus*, in which case it is also called crystallized strophanthin, or g-strophanthin Thoms.

Actions and Uses.—The pharmacologic action of crystallized ouabain is probably qualitatively identical to that of the official strophanthus or strophanthin, but the crystallized ouabain is more active than the official strophanthin when injected subcutaneously or intravenously. This action develops more rapidly, the drug is more quickly excreted, and shows less tendency to cumulative action than does digitalis.

Crystallized ouabain is used in place of strophanthus or strophanthin as a substitute for digitalis.

Dosage.—Ouabain is absorbed so slowly and so irregularly from the alimentary canal that the oral administration of the drug is not to be recommended and is even considered unsafe.

For intravenous or intramuscular administration, the dose is 0.0005 Gm. (1⁄120 grain) and this dose should not be repeated as a rule within less than twenty-four hours. It is best employed dissolved in from 4,000 to 8,000 parts of physiologic solution of sodium chloride. When the intramuscular or intravenous dose is to be repeated within less than twenty-four hours, a smaller amount should be administered.

Since ouabain solution may deteriorate rapidly, only recently prepared solutions or solutions which have been recently tested should be used.

Ouabain Ampules-H. W. & D.: One cubic centimeter of solution contains crystallized ouabain, 0.5 mg. Each ampule contains more than 1 cc. The date of manufacture and an expiration date (three months) is placed on each package.

Prepared by Hynson, Westcott & Dunning, Baltimore, Md.

Ampoules Ouabain 0.0005 Gm. (1-128 grain)-Lilly: Ouabain crystallized 0.0005 Gm. in 2 cc. of a buffered, sterile normal salt solution.

Prepared by Eli Lilly & Company, Indianapolis, Ind.

The light brown dehaired seeds of *Strophanthus gratus* are cold pressed to free them from oil. The oil-free cakes thus formed are broken up and extracted with 96 per cent. alcohol. The alcohol is distilled off on the water bath, leaving a residue, which is thus described: It consists of several layers—an upper thin layer of oil, then an aqueous alcohol layer, followed by a yellowish-brown mass of crystals, under which is a layer of a brown extract, from which an amorphous strophanthin can be isolated. The above mentioned crystals are freed from the mother liquor and recrystallized from hot water. The seeds yield about 3.62 per cent of ouabain.

Ouabain forms colorless quadratic crystals of bitter taste which are easily soluble in hot water, soluble in 100 parts of cold water and 30 parts cold absolute alcohol and 30 parts of amyl alcohol. It is slightly soluble in acetic ether, ether, and chloroform. Its solubilities require further study. Solutions of 1 part of ouabain in 100 parts of 95 per cent. alcohol have been frequently observed to deposit crystals on standing.

A solution of 0.01 Gm. in 1 cc. of water run into a layer of concentrated sulphuric acid colors the latter pink to red and the aqueous layer is colored a dirty green. When crystallized ouabain is dried at 105 C., it should lose from 18 to 22 per cent of water and the anhydrous ouabain so obtained should melt at from 187 to 188 C. On ignition no weighable residue should remain. Heating with dilute hydrochloric acid or sulphuric acid produces hydrolytic cleavage, yielding a body which is identical to rhamnose.

Ouabain-Merck (G. Strophanthin).—A brand of ouabain, crystallized-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

STROPHANTHIN.—**Strophanthinum.**—For description see U. S. Pharmacopeia and Useful Drugs.

Hypodermic Tablets Strophanthin 1/100 grain-Lilly: prepared by Eli Lilly & Company, Indianapolis, Ind.

Hypodermic Tablets Strophanthin 1/120 grain-Lilly: prepared by Eli Lilly & Company, Indianapolis, Ind.

Hypodermic Tablets Strophanthin 1/200 grain (0.325 mg.)-S. & D.: prepared by Sharp & Dohme, Baltimore, Md.

Digitalis Preparations

DIGIPOTEN.—A mixture of the digitalis glucosides in soluble form, diluted with milk-sugar to give the preparation an activity equal to that of digitalis of standard quality as determined by the U. S. Pharmacopeia. It is standardized by the "one hour frog method." The minimum lethal dose of digipoten per gram of body weight of frog is 0.0006 Gm.; or the equivalent in digipoten of 0.0005 mg. of ouabain for each gram of body weight of frog. It is virtually free from digitosaponin.

Actions and Uses.—Digipoten has the same activity as digitalis leaf of good quality and may be used as is the official drug with respect to indications and dosage.

Dosage.—The same as that of digitalis.

Manufactured by The Abbott Laboratories, North Chicago. No U. S. patent or trademark.

Digipoten Tablets: digipoten 0.03 Gm. (½ grain).

Digipoten is prepared by extracting digitalis leaves with diluted alcohol, the alcohol being removed by distillation *in vacuo,* the resulting extract filtered, and the filtrate precipitated with tannin. The precipitated tannates of the glucosides are washed with water, and the glucosides are liberated in the usual manner. The resulting green brittle powder is triturated with sufficient milk sugar to reduce the activity of the finished product to the standard.

Digipoten is a pale green powder, possessing the characteristic bitter taste of digitalis. It is soluble in water and in 25 per cent alcohol.

On ignition it leaves no appreciable amount of ash. If 0.1 Gm. of digipoten is dissolved in 2 cc. of glacial acetic acid containing a trace of ferric chloride and underlaid with concentrated sulphuric acid, there appears at first a brownish zone, changing to red, and finally the upper layer changes to a dark green (*digitoxin*).

DIGITAN.—First introduced as digipuratum.—A digitalis preparation said to contain digitoxin and digitalin in the form of tannates. It is standardized biologically by the method of Gottlieb. It is claimed that in digitan 85 per cent of the inactive substances found in the ordinary extract have been removed and that it is free from digitonin.

Actions and Uses.—The same as those of digitalis.

Dosage.—The same as that of digitalis.

Manufactured by Merck & Co., Inc., Rahway, N. J., under U. S. patent 943,578 (Dec. 4, 1909; expired 1926) by license of the U. S. Federal Trade Commission.

Digitan Ampules (for Hypodermic Use): Each contains 16 minims (1 cc.) of a sterilized solution of digitan equivalent to digitan, 1½ grains (0.1 Gm.).

Digitan Tincture: 1 cc. contains digitan, 1½ grains (0.1 Gm.).

Digitan Tablets, 1½ grains (0.1 Gm.).

Digitan is obtained by removing objectionable constituents from an alcoholic extract of digitalis, neutralized with alkaline hydroxides, by the addition of ether, petroleum benzene, or some other suitable precipitant, and reducing the purified liquid to a powder by evaporating with milk sugar.

Digitan is a greenish-yellow, odorless, bitter powder. The active constituents of digitan are insoluble in cold water and diluted acids, but are easily soluble in weak alkalis.

Digitan responds to the following identity test: If 0.1 Gm. of digitan is underlaid with about 3 cc. of glacial acetic acid which contains 1 per cent of a 5 per cent solution of ferric sulphate, there appears a red band (presence of *digitalin*) and above this another, at first bright green, later changing to dark green and finally blue (presence of *digitoxin*).

The physiologic activity is determined by the method of Gottlieb The activity being adjusted so that the injection into the femoral lymphatic of a freshly caught land frog (*Rana temporaria*), weighing 30 Gm., of 0.2 cc. of a solution made by treating 1 Gm. of digitan with 19 cc. of hot water and 1 cc. of a 2 per cent solution of sodium bicarbonate, causes permanent stoppage of the heart within half an hour in the majority of cases.

DIGITOL.—Fat-Free Tincture of Digitalis-Mulford.—A biologically standardized, fat-free tincture of digitalis, corresponding in drug strength to tincture of digitalis-U. S. P., and containing not more than 70 per cent alcohol.

Actions and Uses.—The same as those of digitalis. Digitol was introduced at a time when the "fat" of digitalis was believed to cause gastric disturbances. At present this claim of superiority is not tenable and the preparation is sold simply as a standardized tincture of digitalis.

Dosage.—From 0.3 to 1 cc. (5 to 15 minims).

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

Digitalis which has previously been subjected to percolation with petroleum benzin is extracted by percolation with the hydro-alcoholic menstruum in the usual way.

It is a brownish-green liquid having a characteristic and highly alcoholic odor and a bitter taste.

It is standardized to such a strength that the minimum lethal dose for a 250 Gm. guinea-pig is approximately 1 cc.

DIGITALIS DISPERT.—An extract of digitalis, obtained by extraction of digitalis leaves with cold water and evaporation of the extraction by a special process, which insures instantaneous drying. It is standardized by the minimum lethal dose frog method of Straub (*Arch. f. exper. Path. u. Pharmakol.* **80**:52, 1916-1917) so that 1 Gm. represents 1,900 lethal frog doses.

Actions and Uses.—Those of digitalis. It is the aim of the manufacturer to offer in digitalis dispert the entire water soluble activity of digitalis glucosides closely resembling their state and proportion in the leaf.

Dosage.—0.08 Gm. (1⅕ grains) from three to six times daily. Digitalis dispert is supplied in the form of tablets only.

Manufactured by Krause Medico Gesellschaft m. b. H., Munich, Germany (Schering & Glatz, Inc.; Bloomfield, N. J., and New York, N. Y., distributor). No U. S. patent. U. S. trademark 194,834.

Digitalis Dispert Tablets 0.08 Gm.: Each tablet represents 150 lethal frog doses.

Digitalis dispert is prepared by extracting specially harvested, air-dried, digitalis leaves with cold water by a special maceration process. The solution thus obtained is brought to dryness by a special spray process of evaporation.

Digitalis dispert is a light brown powder of somewhat aromatic odor and bitter taste.

DYES

The dyes which have been introduced in medicine, for the most part in the last decade, are practically all organic synthetics. Roughly they may be divided into five classes: (1) the azo dyes, of which scarlet red medicinal, scarlet red sulphonate and dimazon are described in New and Nonofficial Remedies (these have been in use for considerable time); (2) the acridine dyes, such as acriflavine hydrochloride (introduced as "acriflavine"), acriflavine base (introduced as "neutral acriflavine") and proflavine; (3) the flourescein dyes, either as flourescein or combined with the metal mercury, such as mercurochrome-220 soluble and flumerin; (4) the phenolphthalein dyes such as phenolphthalein and phenolsulphonphthalein, which are official in the U. S. Pharmacopeia, and the chlorine bromine and iodine substitution products; (5) the triphenylmethane or rosaniline series, which comprise a large list of substances used in the industries, extensively in laboratory practice and more recently in medicine, such as gentian violet, crystal violet, methyl violet and fuchsin; (6) miscellaneous dyes, such as methylene blue (Methylthionine Chloride U. S. P.). Much confusion has existed concerning the composition of dyes, various manufacturers of commercial dyestuffs making similar dyes of varying composition both qualitatively and quantitatively; usually the commercial dye contains a diluent, such as dextrin or salts, and is judged by tinctorial power. In order to obtain comparable results when employed clinically, the dyes should be of constant composition, preferably without diluent.

The Azo Dyes

The azo dyes have been used in medicine for many years—more generally recalled under the name "scarlet R." The exact constitution of the "scarlet R" dyes which have been used seems to have varied in minor details with different investigators. Chemically they have been azo compounds (that is, they contain the linkage—N : N—) combined with betanaphthol. In New and Nonofficial Remedies, a distinction between two scarlet R compounds has been made; scarlet R medicinal Biebrich is described as toluylazotoluylazobetanaphthol; scarlet red sulphonate is described as the sodium salt of azobenzenedisulphonic acid azobetanaphthol; it differs from the former in that the methyl group (CH_3—) of toluyl radicals has been replaced by sodium sulphonate (—SO_3Na) groups.

In addition to the scarlet R compounds is the chemically related diacetylamidoazotoluene (dimazon); this contains only one azo group and has a diacetylamido [$(CH_3CO)_2N$—] group.

Actions and Uses.—Scarlet R medicinal Biebrich and scarlet red sulphonate have a marked power of stimulating the proliferation of epithelial cells.

Opinions are divided as to the clinical value, but the dyes are used to promote the growth of epithelium in the treatment of burns, wounds, chronic ulcers, etc. In chronic ulcers, however, it is requisite that the local circulation be good in order to obtain a permanent result.

Dosage.—The scarlet R preparations are generally used in the form of an ointment containing from 4 to 8 per cent of the substance. The 8 per cent ointment is somewhat irritating and should be alternated with a soothing ointment. Dimazon is generally used in the form of a 2 per cent ointment; it is also employed as a dusting powder (mixed with talcum) or as a solution (in oil).

SCARLET R MEDICINAL BIEBRICH.—Rubrum Scarlatinum. — Toluylazotoluylazo-β-naphthol. — $CH_3C_6H_4N:N C_6H_3.CH_3N:N.C_{10}H_6.OH$.—A compound of betanaphthol and diazotised amidoazo-*o*-toluol.

Actions, Uses and Dosage.—See preceding article, The Azo Dyes.

Biebrich scarlet R medicinal is a dark brownish-red powder, nearly insoluble in water, slightly soluble in benzene and acetone and easily soluble in chloroform, oils, fats and phenols. It is slightly soluble in cold alcohol, somewhat more soluble in hot alcohol, while warm petrolatum and paraffin dissolve rather large quantities. When heated to 175 C., it softens; it begins to melt at from 181 to 188 C.; and at 260 C. it swells up and decomposes. Further heating yields heavy brown, aromatic vapors, which burn, leaving a difficultly but completely combustible residue. The saturated aqueous solution is of a clear scarlet red color, which on dilution or in thin layers has a bluish tinge. It is decomposed by nitroic acid.

If about 1 mg. of Biebrich scarlet R medicinal is sprinkled on about 1 cc. of concentrated sulphuric acid, it will dissolve in the acid with a bluish-green color, which, on diluting with water, changes consecutively to blue, then to purple and finally to red: after a time, a brown flocculent precipitate gradually forms. If to a small quantity of Biebrich scarlet R medicinal a few cubic centimeters of alcohol and 2 drops of hydrochloric acid is added and the mixture boiled, the solution will take on a purple color. This solution on the addition of a few drops of glacial acetic acid becomes scarlet red. If not too small a quantity of the substance was taken, it will crystallize out of the acetic acid solution in the form of fine needles. If about 0.5 Gm. Biebrich scarlet R medicinal is heated to boiling with from 2 to 3 cc. of acetic acid and then, while boiling, zinc dust is added, the solution will become colorless: a bluish color appears on exposure of this solution to air.

Scarlet R Medicinal-Kalle.—A brand of scarlet R medicinal Biebrich-N. N. R.

Manufactured by Kalle & Co., Aktiengesellschaft, Biebrich a/Rh., Germany (Heilkraft Medical Company, Boston). No U. S. patent or trademark. Sold in the form of ointment only.

Scarlet R Salve: Biebrich scarlet R medicinal-Kalle & Co. 8 parts, eucalyptol 2 parts and petrolatum 90 parts.

Prepared by the Heilkraft Medical Company, Boston.

Scarlet R Medicinal Biebrich-Merck.—A brand of scarlet R medicinal Biebrich-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.

Scarlet Red Medicinal-"National."—A brand of scarlet R medicinal Biebrich-N. N. R.

Manufactured by the National Aniline and Chemical Co., New York. No U. S. patent or trademark.

SCARLET RED SULPHONATE.—The sodium salt of azobenzenedisulphonicacid azobetanaphthol. — $C_6H_4.(SO_3Na)N:N.C_6H_3.(SO_3Na).N:N.C_{10}H_6OH$.

Actions, Uses and Dosage.—See preceding article, The Azo Dyes. Scarlet red sulphonate is marketed only in the form of ointment and emulsion.

Manufactured by Badische Anilin und Sodafabrik, Ludwigshafen, Germany (Parke, Davis & Co., Detroit, distributor). No U. S. patent or trademark.

Scarlet Red Emulsion, 4 per cent-P. D. & Co.: scarlet red sulphonate, 4 parts; alcohol, 4 parts; sterilized quince seed jelly, 92 parts.

Scarlet Red Ointment, 5 per cent-P. D. & Co.: scarlet red sulphonate, 5 parts; petrolatum containing a small amount of wax, 95 parts.

Scarlet Red Ointment, 10 per cent-P. D. & Co.: scarlet red sulphonate, 10 parts; petrolatum containing a small amount of wax, 90 parts.

Scarlet red sulphonate is a dark, brownish-red powder; odorless. It is soluble in water; slightly soluble in ether, alcohol and acetone; almost insoluble in chloroform, benzene, fixed oils, fats and petrolatum.

Add diluted hydrochloric acid to a concentrated, aqueous solution of scarlet red sulphonate: red floccules separate from the orange red solution. Add sodium hydroxide solution to a concentrated aqueous solution of the substance: a brownish-red precipitate forms. Treat the substance with concentrated sulphuric acid: a green solution results which becomes blue on the addition of water, and on further dilution, brownish-red floccules separate. Dissolve about 0.1 Gm. of the substance in 5 cc. of glacial acetic acid, heat to boiling, add zinc dust and continue the boiling: the liquid becomes almost colorless.

DIMAZON. — Diacetylamidoazotoluene. — $CH_3.C_6H_4.N:N.C_6H_3(CH_3)N(CH_3CO)_2$.

Actions, Uses and Dosage.—See preceding article, The Azo Dyes.

Manufactured by Kalle & Co., Aktiengesellschaft, Biebrich, a/Rh., Germany (Heilkraft Medical Company, Boston, Mass.). U. S. patent applied for. U. S. trademark 89,119.

Dimazon Ointment: dimazon 2 parts and petrolatum 98 parts.

Prepared by Heilkraft Medical Company, Boston. No U. S. patent or trademark.

Dimazon Oil: dimazon 2 parts and olive oil 98 parts.

Prepared by Heilkraft Medical Company, Boston. No U. S. patent or trademark.

Dimazon Powder: dimazon 5 parts and talcum 95 parts.

Prepared by Heilkraft Medical Company, Boston. No U. S. patent or trademark.

Dimazon is prepared by the acetylization of amido-azotoluene. It is an orange colored crystalline powder, insoluble in water but readily soluble in alcohol, ether, chloroform, acetone and benzene, oils, fats and petrolatum. It can be removed from cloth by washing with soap and water. It melts at 75 C.

When hydrolyzed with a dilute alcoholic solution of sodium hydroxide, dimazon loses an acetyl group with formation of the insoluble monoacetylamidoazotoluol, which has a melting point of 186 C. Prolonged treatment with an alcoholic alkali solution results in loss of the second acetyl group with formation of amidoazotoluol, melting point 100 cc.

Treated with fuming hydrochloric acid, dimazon yields monoacetylazotoluol which is precipitated on dilution with water. Prolonged heating with the acid forms amidoazotoluol and eventually the hydrochloride of the latter.

If dimazon is boiled with alcohol for a long time, an acetyl group is removed with formation of ethyl acetate, which may be recognized by its odor.

The Acridine Dyes

The acridine derivatives are mostly yellow dyes—acridine dyes obtained from coal tar—to which the term "flavine" has been applied ("flavine" should more correctly be applied to a vegetable coloring matter). The representative acridine dyes used in medicine are acriflavine hydrochloride (introduced as "trypaflavine" and "acriflavine"), acriflavine base (introduced as "neutral trypaflavine" and "neutral acriflavine"), and proflavine. In 1912, Ehrlich found that the acridine dye diaminomethylacridinium chloride hydrochloride possessed therapeutic properties when used in trypanosome infections and hence he termed it *trypaflavine*. Later this substance was investigated in England, particularly in regard to its effects as a wound antiseptic, and the name "acriflavine" was applied to it. In a generic sense the terms "trypaflavine" and "acriflavine" have been applied both to acriflavine base and acriflavine hydrochloride. Another closely related substance, diaminoacridine monohydrogen sulphate, was studied also, to which was given the name "proflavine." A considerable number of bacteriologic and clinical reports on these substances have been published. It appears to be established that these dyes possess marked antiseptic and germicidal properties, and on this account, they have been employed in a number of pathologic conditions.

Actions and Uses.—The antiseptic or bacteriostatic action of acriflavine hydrochloride and proflavine appears to be weakened in the presence of serum. In the treatment of wounds, it is claimed that these drugs are comparatively free from toxic or irritant action on living tissues and that they do not inhibit appreciably the phagocytic action of the leukocytes on the healing process. Acriflavine hydrochloride is claimed to exert a specific bactericidal action on the gonococcus. The evidence indicates that it has a greater antiseptic action than proflavine, though its action is slower. Applications of acriflavine hydrochloride, acriflavine base and proflavine have been employed in the treatment of wounds, urethritis, gingivitis, gonorrheal conjunctivitis, blenorrhea, eczema, furunculosis, otitis media, and other conditions requiring the use of a germicide. When taken by mouth, the dyes tend to render the urine antiseptic provided the reaction of the secretion be alkaline. The use of acriflavine base rather than acriflavine has been suggested in areas where freedom from irritation (due to the acid reaction of acriflavine hydrochloride and proflavine) is desirable. The intravenous use of neutral acriflavine has been proposed, but critical evidence for its necessity is lacking.

Dosage.—In the treatment of wounds, the solution generally employed is 1 in 1,000 in physiological solution of sodium chloride, although weaker solutions may be used. In suppurating wounds, this solution is used for syringing and swabbing the wound after free incision, for irrigation after providing adequate drainage, and for saturating the gauze with which the wound is finally covered. Evaporation should be prevented by protective dressing. In cavities, gauze saturated with the solution may be used as a light packing. Fresh wounds are cleansed thoroughly with the solution, and as much of the solution as possible is left in contact with the injured surfaces. Such wounds may be closed by suture and may be expected to heal by first intention.

In the treatment of open wounds, an ointment has been used which contains 1 per cent of proflavine oleate (prepared from proflavine base) in an ointment base composed of equal parts of petrolatum and calcium carbonate. A thick layer of the ointment may be spread on gauze and applied to the surface of the cleansed wound, or the ointment may be spread on the wound directly. The primary dressing need not be changed for several days.

In gonorrhea, a strength of 1 in 1,000 in physiological solution of sodium chloride may be used for injection into the urethra. For irrigation, when relatively large quantities are to be used, a 1 in 4,000 solution is preferable because it is less irritating; solutions of from 1 in 6,000 to 1 in 10,000 have been used. In throat infections a spray of 1 in 1,000 solution is used. In middle ear suppurations a 1 in 500 solution in 50 per cent alcohol is dropped into the ear or the cavity may be packed with gauze wet with the solution. In gingivitis the mouth is irrigated with a 1 in 1,000 solution. Solutions of acriflavine hydrochloride, acriflavine base and proflavine may be boiled, or heated in an autoclave to 130 C., without decomposition, but they are sensitive to light and should be stored in amber bottles. Solutions over a week old should be discarded.

ACRIFLAVINE HYDROCHLORIDE.—Acriflavinae Hydrochloridum.—Acriflavine.—*3: 6* diamino-*10*-methylacridinium chloride monohydrochloride.—*2: 8* diamino-*N*-methylacridinium chloride hydrochloride.

Action, Uses and Dosage: See preceding article, The Acridine Dyes.

Acriflavine hydrochloride is a brownish-red, odorless crystalline powder. It is soluble in about 3 parts of water and in alcohol; nearly insoluble in ether, chloroform, liquid petrolatum, fixed and volatile oils; the solutions are dark red in color and fluoresce on dilution; an aqueous solution (1-250) is distinctly acid when measured by means of the hydrogen electrode.

Add a few drops of hydrochloric acid to an aqueous solution of acriflavine hydrochloride which is just sufficiently diluted to be fluorescent: the fluorescence disappears, but partially reappears on further dilution with water; add 2 drops of sulphuric acid to about 1 cc. of an aqueous solution (1 in 250) and agitate the mixture: an orange-red crystalline precipitate is produced. An aqueous solution (1 in 5) when mixed with an equal volume of a saturated sodium bicarbonate solution produces a marked effervescence (*distinction from acriflavine base*). Dissolve 1 Gm., in 250 cc. water; to a 10 cc. portion add 1 cc. diluted hydrochloric acid; add 1 cc. barium chloride solution: no precipitation occurs (*distinction from proflavine*); to another portion of 10 cc. add 1 cc formaldehyde solution: no precipitation occurs (*distinction from proflavine*).

When tested for arsenic according to the U. S. Pharmacopoeia X., the product should meet requirements for the test for arsenic (p. 428, Arsenic Test). Dry about 1 Gm., accurately weighed, to constant weight over sulphuric acid in a partial vacuum: the loss does not exceed 7 per cent. Incinerate about 1 Gm., accurately weighed, previously dried over sulphuric acid: the ash does not exceed 1 per cent. Dissolve about 1 Gm., accurately weighed, previously dried over sulphuric acid, in 250 cc. of warm water; collect the insoluble matter, if any, in a weighed Gooch crucible; wash the insoluble matter with hot water, dry and weigh the residue: the insoluble matter does not exceed 0.5 per cent.

The nitrogen content determined according to the method described under acriflavine base corresponds to not less than 13.7 per cent, nor more than 14.3 per cent., when calculated to the dried substance. The chlorine content, determined according to the method described under acriflavine base corresponds to the percentage of nitrogen found multiplied by the factor 1.688 (N to Cl in $C_{14}H_{14}N_3$ Cl.HCl) plus or minus 1 per cent., when calculated to the dried substance. Transfer about

0.5 Gm., accurately weighed, to a 400 cc. beaker, and dissolve in 100 cc. of water: the hydrogen chloride content determined by titration with tenth normal sodium hydroxide solution using the hydrogen electrode and a calomel cell (normal potassium chloride solution) corresponds to not less than 12.0 per cent., nor more than 12.5 per cent., hydrogen chloride, when calculated to the dried substance.

Acriflavine-Abbott.—A brand of acriflavine hydrochloride-N. N. R.

Manufactured by The Abbott Laboratories, North Chicago, under U. S. patent 1,005,176 (Oct. 10, 1911; expires 1928), by license of Chemical Foundation, Inc.

Tablets Acriflavine-Abbott, 0.03 Gm.: Each tablet contains acriflavine-Abbott, 0.03 Gm. (0.46 grain).

Acriflavine-"National."—A brand of acriflavine hydrochloride-N. N. R. In addition, acriflavine-"National" is controlled biologically so that the maximum non-lethal dose for mice weighing 20 Gm. shall not exceed 0.0015 Gm.

Manufactured by the National Aniline & Chemical Co., New York, under U. S. patent 1,005,176 (Oct. 10, 1911; expires 1928), by license of The Chemical Foundation, Inc.

To determine the maximum non-lethal dose the drug is dissolved in water in such concentration that 1 cc. contains the quantity to be administered. A series of mice weighing 20 Gm. each are injected subcutaneously with small doses of the drug, each succeeding animal receiving an increase of 1⁄10 mg. of drug over the preceding one. The dosage under which all of the animals survive and over which all die is the maximum non-lethal dose.

ACRIFLAVINE BASE.—Neutral Acriflavine.—The base *3:6*-diamino-*10*-methylacridinium chloride.—*2:8* diamino-*N*-methylacridinium chloride.

Action, Uses and Dosage: See preceding article, The Acridine Dyes.

Acriflavine Base is a brownish-red, odorless, granular powder. It is soluble in about 3 parts of water; incompletely soluble in alcohol; nearly insoluble in ether, chloroform and the fixed oils; the aqueous solution is brownish-red in color, and fluoresces on dilution.

Add a few drops of hydrochloric acid to an aqueous solution of acriflavine base which is sufficiently diluted to be fluorescent: the fluorescence disappears, but partially reappears on further dilution with water. Add 2 drops of sulphuric acid to about 1 cc. of an aqueous solution (1 in 250) and agitate the mixture: an orange-red crystalline precipitate is produced. An aqueous solution (1 in 5) does not effervesce on the addition of an equal volume of a saturated solution of sodium bicarbonate (*distinction from acriflavine hydrochloride and proflavine*). Dissolve 1 Gm. in 250 cc. water; to a 10 cc. portion add 1 cc. diluted hydrochloric acid, add 1 cc. barium chloride solution: no precipitation occurs (*distinction from proflavine*); to another portion of 10 cc. add 1cc. formaldehyde solution: no precipitation occurs (*distinction from proflavine*).

When tested for arsenic according to the U. S. Pharmacopoeia X., the product should meet requirements for arsenic (p. 428, Arsenic Test). Dry about 1 Gm., accurately weighed, to constant weight at 100 C.: the loss does not exceed 7.0 per cent. Dissolve about 1 Gm., accurately weighed, previously dried at 100 C., in 250 cc. of warm water, collect the insoluble matter, if any, in a weighed Gooch crucible, wash the insoluble matter with hot water, dry and weigh the residue: the insoluble matter does not exceed 0.5 per cent. Heat with an excess of sulphuric acid at a low temperature about 1 Gm., accurately weighed, previously dried at 100 C.: the "sulphated" ash does not exceed 3.5

per cent., when calculated as sodium chloride. Transfer about 0.3 Gm., accurately weighed, to a 500 cc. Kjeldahl flask, and determine the nitrogen content according to the method described in Medical War Manual No. 6, Laboratory Methods of the United States Army, p. 221. (The sulphuric acid digestion should be carried on at least 20 hours): the percentage of nitrogen corresponds to not less than 15.5 per cent, nor more than 16.3 per cent., when calculated to the dried substance.

Transfer about 0.25 Gm., accurately weighed, to a 250 cc. Erlenmeyer flask, dissolve in 10 cc. of water, add about 0.5 Gm. of silver nitrate, previously dissolved in about 10 cc. of water; add 10 cc. sulphuric acid, finally add about 2 Gm. of powdered potassium permanganate in several portions; allow the flask and contents to digest on a steam bath for at least 30 minutes; decolorize the solution by addition of hydrogen peroxide with the aid of heat, to remove traces of the manganese oxides formed; filter the precipitate of silver chloride on to a Gooch crucible, wash the precipitate with nitric acid and water, and dry to constant weight at 105 C.: the percentage of chloride corresponds to not less than the percentage of nitrogen found according to the preceding assay multiplied by the factor 0.844 (N to Cl in $C_{14}H_{14}N_3$ Cl), when calculated to the dried substance, nor more than the percentage of nitrogen found times 0.844 plus 3.0 per cent., when calculated to the dried substance. Transfer about 0.5 Gm., accurately weighed, to a 400 cc. beaker, and dissolve in 100 cc. of water: the hydrogen ion concentration determined by using the hydrogen electrode and a calomel cell (normal potassium chloride solution) corresponds to a *p*H of not less than 3 nor more than 7.

Neutral Acriflavine-Abbott.—A brand of acriflavine base-N. N. R.

Manufactured by The Abbott Laboratories, North Chicago, under U. S. patent 1,005,176 (Oct. 10, 1911; expires 1928) by license of the Chemical Foundation, Inc. No U. S. trademark.

Enteric Coated Tablets Neutral Acriflavine-Abbott, 0.03 Gm. (½ grain). Each contains neutral acriflavine-Abbott 0.03 Gm. (½ grain), and is coated with shellac and phenyl salicylate.

Neutral Acriflavine-Abbott for Intravenous Injection, 0.1 Gm. Ampules.

Neutral Acriflavine Jelly 1:.1,000-Abbott: Neutral acriflavine-Abbott, 0.1 part, dissolved in karaya gum jelly, containing sufficient sodium hydroxide so that the finished product has a *p*H of about 8.5, to make 100 parts.

Tablets Neutral Acriflavine-Abbott, 0.03 Gm. (½ grain).

Neutral Acriflavine-"National."—A brand of acriflavine base-N. N. R.

Manufactured by The National Aniline and Chemical Co., New York, under U. S. patent 1,005,176 (Oct. 10, 1911; expires 1928) by license of the Chemical Foundation, Inc. No U. S. trademark.

Enteric Coated Tablets Neutral Acriflavine-"National," 0.0324 Gm. (½ grain): Each contains neutral acriflavine-"National" 0.0324 Gm. (½ grain), and is coated with phenyl salicylate containing some keratin.

Tablets Neutral Acriflavine-"National," 0.1 Gm. (1½ grains).

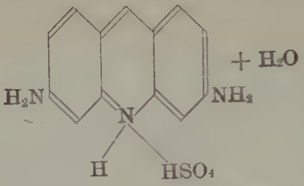
Neutral Acriflavine-"National" Troches: Each contains neutral acriflavine-"National," 0.006 Gm., menthol 0.0006 Gm. and sodium chloride 0.0006 Gm.

Neutral Acriflavine-"National" "Pro Injectione," 0.5 Gm. vials.

Neutral Acriflavine-"National" "Pro Injectione," 1.0 Gm. vials.

Ointment Neutral Acriflavine-"National," 1 per cent: Neutral Acriflavine-"National," 1 part, dissolved in glycerin, 8 parts, and incorporated with a base composed of hydrous wool fat and petrolatum to make 100 parts.

PROFLAVINE. — Proflavina. — 3:6-diaminoacridinium monohydrogen sulphate.—2:8-diaminoacridinium monohydrogen sulphate.



Actions, Uses and Dosage.—See preceding article, The Acridine Dyes.

Proflavine is a reddish-brown, odorless, crystalline powder. It is soluble in water and in alcohol, forming brownish solutions which fluoresce on dilution; it is nearly insoluble in ether, chloroform, liquid petrolatum, fixed oils and volatile oils.

An aqueous solution of proflavine is neutral to litmus. Add a few drops of hydrochloric acid to an aqueous solution of proflavine which is sufficiently dilute to be fluorescent. The fluorescence disappears, but partially reappears on dilution with water. Add 2 drops of sulphuric acid to about 1 cc. of an aqueous solution of proflavine (1 in 250), and agitate the mixture. A brown, crystalline precipitate is produced. Under the microscope the crystals are seen to be mostly prismatic needles. An aqueous solution of proflavine (1 in 250) gives a precipitate with barium chloride solution (*distinction from acriflavine*). An aqueous solution of proflavine (1 in 250) gives no precipitate with silver nitrate solution (*distinction from acriflavine*). Add a few drops of formaldehyde solution to 5 cc. of an aqueous solution of proflavine (1 in 250), and immediately add 2 drops of sodium nitrite solution (1 in 10). A violet color is produced. On the further addition of sodium nitrite solution, a brownish violet precipitate is formed and, after a few minutes, the solution becomes colorless. This may be best observed after filtration (*distinction from acriflavine, the filtrate from which becomes cherry-red*). An aqueous solution of proflavine (1 in 250) gives a lemon yellow precipitate with sodium hydroxide solution (*distinction from acriflavine, which gives an orange precipitate*).

Incinerate about 1 Gm. of proflavine, accurately weighed: the ash amounts to not more than 1 per cent.

Dissolve about 1 Gm. of proflavine, accurately weighed, in 250 cc. of warm water, collect the insoluble matter, if any, in a weighed Gooch crucible, wash the insoluble matter with hot water, dry and weigh the residue: the insoluble matter amounts to not more than 1 per cent.

Dry about 1 Gm. of proflavine, accurately weighed, to constant weight at 100 C.: the substance loses not more than 10 per cent of its weight.

Proflavine-Abbott.—A brand of proflavine-N. N. R.

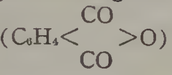
Manufactured by The Abbott Laboratories, North Chicago, under U. S. patent 1,005,176 (Oct. 10, 1911; expires 1928), by license of The Chemical Foundation, Inc.

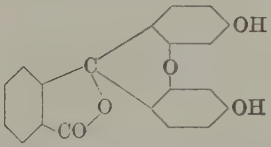
Proflavine-"National."—A brand of proflavine-N. N. R. In addition, proflavine-"National" is controlled biologically so that the maximum non-lethal dose for mice weighing 20 Gm. must not exceed 0.006 Gm.

Manufactured by the National Aniline & Chemical Co., New York, under U. S. patent 1,005,176 (Oct. 10, 1911; expires 1928), by license of The Chemical Foundation, Inc.

To determine the maximum non-lethal dose the drug is dissolved in water in such concentration that 1 cc. contains the quantity to be administered. Of a series of mice weighing 20 Gm. apiece, each is injected subcutaneously with small doses of the drug, each succeeding animal receiving an increase of 1/10 mg. of drug over the preceding one. The dosage under which all of the animals survive and over which all die is the maximum non-lethal dose.

The Fluorescein (Pyronine) Dyes

Fluorescein is formed by combining resorcinol ($C_6H_4(OH)_2$) with phthalic anhydride  $(C_6H_4<\begin{matrix}CO\\ \\CO\end{matrix}>O)$; at the same time water is given off yielding a product having the structural formula



The product is closely related to phenolphthalein and its derivatives (which are described in the next section), differing chiefly in the presence of the oxygen molecule between the two ortho positions of the resorcinol nuclei. In common with the phthaleins, it forms salts with alkali whereby a rearrangement takes place and the quinoid group is formed. Fluorescein is easily brominated, the tetrabrom compound being the beautiful dye eosin. Fluorescein has been combined with one molecule of mercury (—HgOH), the sodium salt of which is flumerin; in mercurochrome-220 soluble, two of the hydrogen atoms of flumerin have been replaced by two bromine atoms.

Actions and Uses.—Fluorescein has been employed mainly as a diagnostic agent in ophthalmologic work. Flumerin and mercurochrome-220 soluble are bactericides; flumerin has also been employed in the treatment of syphilis.

FLUORESCEIN.—Fluoresceinum.—Resorcinolphthalein (a term not strictly correct but commonly used).—Dioxyfluoran. —$O:(C_6H_3OH)_2:C.C_6H_4.COO$.—The anhydride of fluoresceinic acid, $O:(C_6H_3OH)_2:C(OH).C_6H_4(COOH)$.

Actions and Uses.—The soluble sodium salt of fluorescein (fluorescein 2 Gm., sodium bicarbonate 3 Gm., water to make 100 cc.) has been used for the diagnosis of corneal lesions and the detection of minute foreign bodies embedded in the cornea. While a weak solution of fluorescein will not stain the normal cornea, ulcers or parts deprived of epithelium will become green and remain so for a time; foreign bodies will appear surrounded by a green ring; loss of substance in the conjunctiva is indicated by a yellow hue. Fluorescein also reveals defects or disease of the endothelium of the cornea, producing a deep coloration of the diseased area.

Fluorescein is prepared by the fusion of phthalic anhydride and resorcinol at from 195 to 200 C. till the mass becomes solid. This is extracted with water and the residue dissolved in potassium hydroxide solution, which is then filtered and the fluorescein precipitated with acid.

Fluorescein is an orange red powder, insoluble in water, ether, chloroform and benzol; soluble in hot glacial acetic acid and boiling alcohol. It dissolves in alkaline solution with formation of a salt. The alkaline solution by transmitted light is red; by reflected light it has a green fluorescence even in very dilute solutions. When fluorescein is boiled with chalk and water, the calcium salt of fluorescein is formed, which is recognized by its red brown color and green sheen.

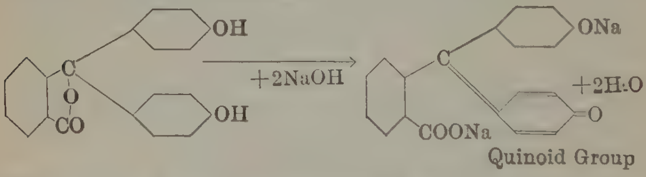
Fluorescein-Merck.—A brand of fluorescein-N. N. R.
Merck & Co., Inc., Rahway, N. J., distributor.

FLUMERIN.—See Mercury and Mercury Compounds.

MERCUROCHROME-220 SOLUBLE.—See Mercury and Mercury Compounds.

The Phenolphthalein Dyes

Phenolphthalein—long used by chemists as an indicator before its therapeutic properties were discovered—is a condensation product of phthalic anhydride and phenol. In neutral and acid mediums it exists in a form in which there is no quinoid group, but the presence of alkali ($p\text{H}=8$ to 10) causes the characteristic rearrangement with typical salt formation and the presence of a quinoid group whereby the beautiful red color is formed.



This reaction is also characteristic of other members of the series. Phenolsulphonphthalein—which chemists also use as an indicator—contains an SO_3 group in place of the CO group in the phthalic anhydride nucleus. In phenoltetrachlorphthalein, the four hydrogen atoms in the benzene ring belonging to the phthalic acid nucleus have been replaced by chlorine; in tetrabromophenolphthalein, the four bromine atoms are in the phenol groups, two in each; this, it will be noted is a different substitution than in the case of phenoltetrachlorphthalein.

Actions and Uses.—All of the compounds of the phenolphthalein type are used in medicine as diagnostic agents except phenolphthalein itself. Also phenolphthalein is used not because of its property of color formation, but because of its action on the intestine. Phenolsulphonphthalein and phenoltetrachlorphthalein are used because they pass unchanged through the body and at the same time have the property of intense color formation when the excretions are collected and alkalinized. Bromsulphalein is used in a somewhat analogous way, but instead of determining the amount in the excretion of the bile, the amount (not excreted) in the blood gives an index of liver function. Tetrabromophenolphthalein and tetraiodophenolphthalein—which are employed in the form of the sodium salts—are not used because they are dyes *per se,* but rather as carriers of bromine or iodine; they appear in the gallbladder in sufficient concentration to permit the heavy halogen molecules to cast a shadow to the roentgen ray.

BROMSULPHALEIN-H. W. & D.—Disodium phenoltetrabromphthaleinsulphonate.—$\underline{O.CO.C_6Br_4.C}[C_6H_3(OH)SO_3Na]_2$.

The disodium salt formed by the interaction of tetrabromophthalic acid (or anhydride) and phenol with subsequent sulphonation. It contains from 37 to 38 per cent of bromine.

Actions and Uses.—Bromsulphalein-H. W. & D., after intravenous injection into normal rabbits, is excreted in the bile to the extent of about 85 per cent in one hour. Normally it is rapidly removed from the blood stream, but when the liver is extirpated it is retained in the blood stream almost completely. In normal animals the drug appears in the urine in traces only or not at all. Experiments on man have been in accord with animal experiments.

Bromsulphalein-H. W. & D. is used as a test of liver function; the amount remaining in the blood stream after intravenous injection, as determined colorimetrically, is considered a measure of hepatic dysfunction.

Dosage.—0.002 Gm. per kilogram of body weight is injected intravenously in 5 per cent aqueous solution without dilution. To carry out the test, the solution of salt may be injected into an arm vein; thirty minutes after the injection, a specimen of blood (from 4 to 5 cc.) is drawn, preferably from the opposite arm, by allowing the blood to run from the needle directly into a dry test tube; after the blood has coagulated it is centrifugalized and the serum is pipetted into two small test tubes; to one of these is added one or two drops of a 10 per cent solution of sodium hydroxide, and to the other tube, a drop of hydrochloric acid; the amount of dye present is determined by comparison with a series of standards.

Manufactured by Hynson, Westcott & Dunning, Baltimore. U. S. patent and trademark applied for.

Solution Bromsulphalein-H. W. & D.: Ampules containing 3 cc. of a sterile 5 per cent solution of bromsulphalein-H. W. & D.

Bromsulphalein-H. W. & D. is a white, crystalline powder, soluble in water, insoluble in alcohol or acetone. The aqueous solution is almost colorless.

To a few cubic centimeters of a 1 per cent solution of bromsulphalein-H. W. & D., add a drop of hydrochloric acid: no precipitate is formed. To 3 cc. of a 1 per cent solution of bromsulphalein-H. W. & D., add a drop of sodium hydroxide solution: an intense bluish purple color results. To 2 cc. of a 1 per cent aqueous solution of the salt, add a drop of hydrochloric acid, heat to boiling and add an equal volume of boiling 1 per cent barium chloride solution: the liquid remains clear while hot (*absence of sulphate*); on cooling, crystals of a difficultly soluble barium salt form which under the microscope appear as groups of platelets (*distinction from barium sulphate*). To a 1 per cent solution of the salt, add an equal volume of 5 per cent calcium chloride solution: no precipitate forms, even after the addition of an equal volume of alcohol. Acidify a 1 per cent solution of the salt with nitric acid and add silver nitrate solution: not more than a slight opalescence is produced (*limit of ionic halogen*). To each of a series of phosphate buffer mixtures from p_H 6.8 to p_H 8.8 of 5 cc. each, add a drop of 5 per cent solution of bromsulphalein-H. W. & D.: there is no color at 6.8; a faint perceptible purple at 7.0; the color increases in intensity up to 8.4.

Determine the bromine content of bromsulphalein-H. W. & D. by the lime or the sodium hydroxide combustion method: the bromine content is from 37 to 38 per cent.

PHENOLSULPHONPHTHALEIN.—For description see the U. S. Pharmacopeia under Phenolsulphonphthaleinum.

Actions and Uses.—Solutions of phenolsulphonphthalein injected into the tissues are readily absorbed, and are excreted mainly in the urine. A very small amount is excreted by the feces.

Phenolsulphonphthalein is used for determining the functional activity of the kidney. When injected intramuscularly or intravenously, it begins to be excreted in normal cases in from five to ten minutes. In case of a deficient functional activity, the first appearance of its secretion is delayed. In normal cases, after intramuscular injections, almost the total amount is excreted within two hours (from 60 to 80 per cent). Failure to excrete nearly the full amount within two hours indicates a deficient functional activity, and the degree of this functional deficiency may be estimated by the proportionate amount excreted within two hours. The average normal eliminations after intravenous administration are from 35 to 45 per cent in fifteen minutes, from 50 to 65 per cent in thirty minutes, and from 65 to 80 per cent in the first hour.

Dosage.—One cc. of a sterile solution, containing 0.006 Gm. of phenolsulphonphthalein as the monosodium salt, is injected into the lumbar muscles. Great care must be taken that all of the solution is injected.

From twenty minutes to half an hour before administering the test, the patient is given from 200 to 400 cc. of water in order to insure free urinary secretion; otherwise delayed time of appearance may be due to lack of secretion.

Under aseptic precautions a catheter is introduced and the bladder is completely emptied, or the patient is allowed to empty it voluntarily. The time is noted, and 1 cc. of a carefully prepared solution of the phenolsulphonphthalein containing 6 mg. to the cubic centimeter is accurately administered intramuscularly or intravenously by means of an accurately graduated syringe.

The urine is allowed to drain into a test tube in which has been placed a drop of 25 per cent sodium hydroxide solution, and the time of the appearance of the first faint pinkish tinge is noted.

In patients having no urinary obstruction, the catheter is withdrawn at the time of the appearance of the drug in the urine. If injection is made *intramuscularly,* the patient is instructed to void into a receptacle at the end of one hour and ten minutes, and into a second receptacle at the end of the second hour. If injection is made *intravenously,* the patient is instructed to void into a receptacle at the end of fifteen or thirty minutes or one hour.

When the passing of a catheter is disagreeable and no urinary retention is present, its use can be dispensed with and the time of appearance of the drug can be disregarded.

The urine collected is made alkaline with a 25 per cent solution of sodium hydroxide and then diluted to 1 liter. The solution is thoroughly mixed and a small filtered portion taken, to compare with the standard which is used for all of these estimations. Comparison is made in a colorimeter, a special form of which has been devised for this purpose.

Phenolsulphonephthalein Ampules-H. W. & D.: **One cc. of solution contains 6 mg. of phenolsulphonphthalein, in the form of the monosodium salt. Each ampule contains more than 1 cc.**

Prepared by Hynson, Westcott & Dunning, Baltimore.

PHENOLTETRACHLORPHTHALEIN-H. W. & D.—**Phenoltetrachlorphthaleinum.**—A dibasic dye formed by the condensation of phenol and tetrachlorphthalic acid or its anhydride.

Actions and Uses.—Phenoltetrachlorphthalein has been used for the determination of the functional activity of the liver. It can be used, *in form of the sodium salt,* intravenously; it cannot be given subcutaneously or intramuscularly. It has been proposed that the excretion can be determined by any one of these methods:

1. The excretion of the drug in the stool: Rowntree, Hurwitz and Bloomfield (*Bull. Johns Hopkins Hosp.* **24**:327, 1913); Whipple, Peightal and Clark (*Bull. Johns Hopkins Hosp.* **24**:343, 1913); Rowntree, Marshall and Chesney (*Proc. Am. A. Phys. & Surg.* 1914; The Journal, Oct. 31, 1914, p. 1533).

2. The excretion of the drug in the duodenum by means of a duodenal tube: Aaron, Beck and Schneider (The Journal, Nov. 19, 1921, p. 1631).

3. Its disappearance from the blood stream: S. M. Rosenthal (*J. Pharmacol. & Exper. Therap.* **19**:385 [June] 1922); H. H. Rosenfield and E. F. Schneiders (The Journal, March 17, 1923, p. 743).

Dosage.—From 0.05 to 0.4 Gm. administered in the form of the disodium salt. The solution must not be exposed unduly long, as the salt is sensitive to the action of the carbon dioxide of the atmosphere.

Manufactured by Hynson, Westcott & Dunning, Baltimore, Maryland. No U. S. patent or trademark.

Ampules Phenoltetrachlorphthalein-H. W. & D.: Each ampule contains more than 2 cc. of a solution of disodium phenoltetrachlorphthalein, each cubic centimeter representing 0.05 Gm. of phenoltetrachlorphthalein-H. W. & D.

Phenoltetrachlorphthalein-H. W. & D. is a cream white powder: odorless; permanent in the air. It is practically insoluble in water; very soluble in acetone; soluble in alcohol, ether and glacial acetic acid; slightly soluble in chloroform, benzene and carbon disulphide. It dissolves in solutions of the alkalies and carbonates to form solutions which are deep purple when concentrated, but which change to violet-red on dilution, and in very dilute solutions assume a bluish tint (*distinction from phenolphthalein*).

Phenoltetrachlorphthalein does not melt when heated to 300 C. It does not respond to the U. S. P. test for heavy metals as described under phenolphthalein.

Dry about 1 Gm. of phenoltetrachlorphthalein-H. W. and D., accurately weighed, to constant weight at 115 C.: the loss is not more than 0.5 per cent. To about 5 Gm. of the substance, accurately weighed, add 25 cc. of normal sodium hydroxide solution, heat to about 70 C. and stir. Dilute with warm water to about 75 cc., filter through a tared Gooch crucible, dry to constant weight at 115 C. and weigh: the weight of the insoluble matter (*tetrachlorfluorane*) does not exceed 0.2 per cent. Incinerate about 2 Gm. of the substance, accurately weighed: the ash does not exceed 0.15 per cent.

PHENTETIOTHALEIN SODIUM.—Phentetiothaleinis Sodium.—Phenoltetraiodophthalein Sodium.—$\mathrm{NaO.O:}\overline{\mathrm{C.C_6I_4.C:C_6H_4OC}}\mathrm{_6H_4ONa}$. The sodium salt of a dibasic dye, phenoltetraiodophthalein. Phentetiothalein sodium contains from 56 per cent to 59 per cent of iodine.

Actions and Uses.—Phentetiothalein sodium is used for the roentgenologic examination of the gallbladder and simultaneous test of hepatic function. Following the intravenous injection, the solution appears in the normal gallbladder in sufficient concentration to cast a shadow to the roentgen rays and if the liver is damaged it is retained in the blood in amounts indicative of the extent of impairment. It is claimed to cause little or no toxic reaction.

Dosage.—Intravenously for visualization of the gallbladder and simultaneous test of liver function, 40 mg. per kilogram of body weight; the dose need not exceed 2.5 Gm., regardless of weight. The dye is dissolved in freshly distilled water, filtered through fine filter paper, and sterilized for fifteen minutes in a boiling water bath. A solution of 8 per cent has been found satisfactory. The solution is injected intravenously by gravity or syringe method, either in the morning between 8 and 9 or in the evening between 5 and 9. If given in the evening the evening meal should be omitted and no food given until the first roentgenogram is taken in the morning. At this time a fat meal is given and the roentgenogram taken one hour after the meal and, if desired, another three hours after the meal to determine the rapidity and characteristics of emptying. More satisfactory results are probably obtained if the injection is made in the morning with the stomach empty, omitting breakfast and lunch and taking roentgenograms four, eight and twenty-four hours after the injection. For gallbladder visualization alone the drug is administered orally: 4 Gm. in the form of plain gelatin capsules (8 capsules of 0.5 Gm. each), or dissolved in 30 cc. of distilled water and added to 120 to 240 cc. of grape juice, to be taken during and after the evening meal, which should be of the usual amount but free of fat (the aqueous solution of the drug should not be more than 48 hours old). Meticulous roentgen ray technic is necessary, and if the interpretation of the cholecystogram is in question a check determination should be made either by the oral or, if preferred, by the intravenous method. The liver function test cannot be made by this method because the dye is not absorbed rapidly enough into the blood.

To make the determination of liver function, blood is collected one-half hour and again preferably one hour after the intravenous injection. The serum is alkalized with a small drop of 5 per cent solution of sodium hydroxide and compared to a set of standard solutions as suggested by Rosenthal (An Improved Method for Using Phenoltetrachlorphthalein as a Liver Function Test, *J. Pharmacol. & Exper. Therap.* **19**:385 [June] 1922) and modified by Cole, Copher and Graham (Simultaneous Cholecystography and Determination of Liver Function, J. A. M. A. **90**:1111 [April 7] 1928).

Phentetiothalein sodium occurs as bronze purple, odorless, slightly hygroscopic granules. It is soluble in water and alcohol.

Dissolve 1 Gm. of phentetiothalein sodium in water: a clear solution appears. Add diluted hydrochloric acid drop by drop to 1 cc. of a 10 per cent aqueous solution of phentetiothalein sodium: a yellow colored precipitate appears. Add sodium hydroxide solution in large excess to 1 cc. of a 10 per cent aqueous solution of phentetiothalein sodium: a permanent purple color appears.

Intimately mix 0.1 Gm. of the salt with 1.0 Gm. of anhydrous sodium carbonate and heat to fusion; cool the mixture, dissolve in diluted hydrochloric acid and filter; add a few drops of hydrogen peroxide solution and agitate the mixture with a few cubic centimeters of chloroform: the chloroform layer is colored violet (*iodine*).

Transfer about 0.5 Gm., accurately weighed, of phentetiothalein sodium to a flat type weighing bottle and dry in a vacuum at 80 C. to constant weight: the loss in weight is not more than 5 per cent.

Transfer about 0.2 Gm., accurately weighed, of phentetiothalein sodium to a bomb tube; determine the iodine by the Carius method: the amount of iodine found is not less than 56 per cent nor more than 59 per cent when calculated to the dry basis.

Iso-Iodeikon.—A brand of phentetiothalein sodium-N. N. R.

Manufactured by the Mallinckrodt Chemical Works, St. Louis. No U. S. patent or trademark.

Iso-Iodeikon, 2.5 Gm. Ampoules.

TETBROTHALEIN SODIUM.—Tetbrothaleinis Sodium. —Tetrabromophthalein Sodium.—Tetrabromophenolphthalein Sodium. — $NaOOC.C_6H_4.C:C_6H_2Br_2O.C_6H_2Br_2ONa$. — The sodium salt of a dibasic dye, tetrabromophenolphthalein. The sodium salt contains about 47 per cent of bromine.

Actions and Uses.—Tetbrothalein sodium is used for the roentgenologic examination of the gallbladder. Following intravenous injection, the substance appears in the gallbladder in sufficient concentration to cast shadows to the roentgen ray. After injection some of the patients may have unpleasant sensations such as dizziness, nausea, various body pains and fall in blood pressure; the transitory fall in blood pressure may be relieved by administration of 0.5 to 1 cc. of epinephrine (1 in 1,000) intramuscularly. The use of tetbrothalein sodium is still in the experimental stage and workers are cautioned as to the selection of types of cases in which it is indicated and its possible toxicity in large doses.

Dosage.—A dose of 0.1 Gm. per Kg. has been found sufficient to cast a shadow. To visualize the gallbladder in the patient, 4.5 to 5 Gm. of tetbrothalein sodium (which has not undergone change by exposure to light) are dissolved in 35 to 40 cc. of freshly distilled water and filtered. The solution is then sterilized by heating the container in boiling water for 20 minutes. This dose is sufficient for a person weighing 125 pounds or more and should be reduced for patients weighing less. The solution is given intravenously with a syringe in two doses, one-half hour apart, in the morning before breakfast. Care should be taken not to allow extravasation on account of tissue necrosis.

Tetbrothalein sodium is a pale blue to purplish blue powder, odorless. It is very soluble in water; its aqueous solution has a reaction of $p\text{H} = 8$ to 10. It is very slightly soluble in alcohol, insoluble in ether.

Dissolve 1 Gm. of tetbrothalein sodium in 4 cc. of water: a clear solution results.

Add diluted hydrochloric acid, drop by drop, to 1 cc. of tetbrothalein sodium solution (1 to 10) until acid; a white precipitate results: add sodium hydroxide solution in great excess: the precipitate dissolves, the purple color first forms, then disappears.

To 1 cc. of an acid solution of tetbrothalein add 2 cc. of bromine water: a yellow precipitate results.

Weigh accurately 0.25 Gm. of the sample and place in a 300 cc. Kjeldahl flask; add exactly 17 cc. of absolute alcohol and connect the flask with a reflux Liebig condenser, cooled with tap water. Warm slightly and begin the introduction of sodium metal. The sodium metal is prepared by rolling 2.3 Gm. of the metal free from surface film between filter paper into small (10-15 pieces) rods. This should be kept in a tightly stoppered weighing bottle during the operation. The sodium is then added through the top of the condenser, one piece at a time. After several pieces have been added, there may be two or three undissolved pieces in the flask at one time. The addition of the sodium should take between 30 and 40 minutes. The solution of the last half of the sodium may require very gentle heating (*caution*). After the sodium is all added, reflux the mixture gently for one hour and then allow to cool. Add water, 1 cc. at a time through the top of the condenser until any sodium is taken up. The flask may then be disconnected and more water added and shaken until the precipitate is completely dissolved. Transfer to a 500 cc. Erlenmeyer flask and dilute to 200 cc.; acidify with 20 per cent nitric acid solution and add 25 cc. of tenth-normal silver nitrate and 2 cc. ferric nitrate indicator solution. Titrate the unconsumed silver nitrate with tenth-normal ammonium sulphocyanate solution: the amount of bromine should not be less than 43.5 per cent.

Bromeikon.—A brand of tetbrothalein sodium-N. N. R.

Manufactured by the Mallinckrodt Chemical Works, St. Louis. No U. S. patent or trademark.

Bromeikon, 5 Gm. Ampules.

Tetrabromophenolphthalein Sodium Salt-Eastman.—A brand of tetbrothalein sodium-N. N. R.

Manufactured by the Eastman Kodak Company, Rochester, N. Y. No U. S. patent or trademark.

TETIOTHALEIN SODIUM.—Tetiothaleinis Sodium.—Tetraiodophthalein Sodium. — Tetraiodophenolphthalein Sodium.—$NaO.O:C.C_6H_4.C:C_6H_2I_2OC_6H_2I_2ONa$. The sodium salt of a dibasic dye, tetraiodophenolphthalein. Tetiothalein sodium contains not less than 53 per cent of iodine.

Actions and Uses.—Tetiothalein sodium is used for the roentgenologic examination of the gallbladder. Following the intravenous injection or, if decomposition is avoided, the oral administration, the substance appears in the normal gallbladder in sufficient concentration to cast a shadow to the roentgen ray. After injection, a few of the patients may have unpleasant sensations, such as dizziness, nausea, various body pains, and fall in blood pressure,. The transitory fall in blood pressure may be relieved by the administration of from 0.5 to 1 cc. of epinephrine hydrochloride solution (1 in 1,000) intramuscularly. Tetiothalein sodium is useful as a diagnostic agent, but workers are cautioned as to the selection of types of cases in which it is indicated and its possible toxicity in large doses. More than 1,000 patients, however, are reported to have been examined by this method with no deaths.

Dosage.—To visualize the gallbladder in a patient weighing between 115 and 160 pounds (52 and 72.6 Kg.), 3 Gm. of tetiothalein sodium is dissolved in 24 cc., or 3.5 Gm. of tetiothalein sodium is dissolved in 28 cc. of freshly distilled water; the solution is then sterilized by heating the container in boiling water for twenty minutes. For patients weighing over 160 pounds the maximum dose should not exceed 3.5 Gm. For patients weighing less than 115 pounds (52 Kg.), the amount of salt is to be reduced. The solution is injected intravenously in two doses, one-half hour apart in the morning before breakfast. Care must be taken not to allow extravasation on account of tissue necrosis. Breakfast is omitted. At noon a glass of milk is permitted, and the evening meal is allowed as usual. Water by mouth is allowed at all times.

Tetiothalein sodium may be administered orally: 4 Gm. in the form of plain gelatin capsules (8 capsules of 0.5 Gm. each), or dissolved in 30 cc. of distilled water and added to 120 to 240 cc. of grape juice, to be taken during and after the evening meal, which should be of the usual amount but free of fat (the aqueous solution of the drug should not be more than 48 hours old). Meticulous roentgen ray technic is necessary, and if the interpretation of the cholecystogram is in question a check determination should be made either by the oral or, if preferred, by the intravenous method.

Tetiothalein sodium is a pale blue to dark blue, somewhat hygroscopic, crystalline powder, odorless. It is soluble in water and in alcohol. The aqueous solution (1: 300) has a reaction of p_H 7 to 9.

Dissolve 1 Gm. of tetiothalein sodium in 10 cc. of water: a clear solution results. Add diluted hydrochloric acid, drop by drop, to 1 cc. of a 10 per cent aqueous solution until the liquid is acid in reaction: a cream colored precipitate is formed. Add sodium hydroxide solution to this mixture in large excess: a purple color first forms and then disappears. Intimately mix 0.1 Gm. of the salt with 1 Gm. of anhydrous sodium carbonate and heat to fusion; cool the fusion and dissolve it in diluted hydrochloric acid and filter; add a few drops of hydrogen peroxide solution and agitate the mixture with a few cubic centimeters of chloroform: the chloroform layer is violet (*iodine*).

Weigh accurately about 0.25 Gm. of tetiothalein sodium in a stoppered weighing bottle. Transfer it to a 300 cc. Kjehldahl flask, add 11 cc. of absolute alcohol and connect the flask with a reflux Liebig condenser cooled with tap water. Warm slightly and begin the introduction of sodium metal. The sodium metal is prepared by rolling 2.3 Gm. of the metal, free from surface film, between paper into small (from ten to fifteen pieces) rods. This should be kept in a tightly stoppered weighing bottle during the operation. The sodium metal is added through the top of the condenser, one piece at a time. After several pieces have been added, there may be two or three undissolved pieces in the flask at one time. The addition of the sodium should occupy between thirty and forty minutes. Gentle heating may be required to dissolve the last pieces of sodium (*caution*). After the sodium has been all added, reflux the mixture for one hour and then allow to cool. Add water, 1 cc. at a time, through the top of the condenser, until the sodium is taken up. Then disconnect the flask and add more water until the precipitate is dissolved. Transfer the liquid to a 500 cc. Erlenmeyer flask and dilute to 200 cc.; acidify with 20 per cent nitric acid solution and add 25 cc. tenth-normal silver nitrate and 2 cc. ferric nitrate indicator. Titrate the unconsumed silver nitrate with tenth-normal ammonium thiocyanate: the amount of iodine found is not less than 53 per cent. (If the weight of salt taken for the assay appreciably exceeds 0.25 Gm., a proportional change in the amount of absolute alcohol and sodium metal must be made.)

Iodeikon.—A brand of tetiothalein sodium-N. N. R.

Manufactured by the Mallinckrodt Chemical Works, St. Louis. No U. S. patent. U. S. trademark 222, 470.

Iodeikon, 3.5 Gm. Ampules.

Iodeikon Capsules-Swan-Myers.—Each keratin coated capsule contains iodeikon, 0.25 Gm.

Prepared by Swan-Myers Co., Indianapolis, Ind.

Tetraiodophenolphthalein Sodium Salt-Eastman.—A brand of tetiothalein sodium-N. N. R.

Manufactured by the Eastman Kodak Company, Rochester, N. Y. No U. S. patent or trademark.

The Triphenylmethane (Rosaniline) Dyes

Of the derivatives of triphenylmethane and its homologue tolyldiphenylmethane, the most interesting medicinally are those which result from the introduction of amino groups forming pararosaniline (triaminotriphenylcarbinol $(NH_2C_6H_4)_3COH$) and rosaniline (triaminodiphenyltolycarbinol $(NH_2C_6H_4)_2(CH_3.NH_2.C_6H_3).COH$). On treating rosaniline with hydrochloric acid, the hydroxyl of the carbinol group is split off, permitting the formation of a quinoid group; thus is formed a typical dye known as fuchsin, $NH_2C_6H_4.CH_3.NH_2.C_6H_3.C:C_6H_4:NH_2.Cl$. The red color of pararosaniline chloride or fuchsin is changed to violet by the entrance of a methyl group in the amino groups, the intensity of the violet color increasing with an increasing number of methyl groups. Thus, there is the closely related gentian violet, crystal violet and methyl violet. Gentian violet is a mixture of pentamethylpararosaniline chloride and hexamethylpararosaniline chloride; by some it is defined as a mixture of methyl violet and crystal violet. Crystal violet is a relatively pure form of hexamethylpararosaniline chloride; methyl violet is considered to contain mostly pentamethylpararosaniline chloride with some of the hexaderivative and probably some tetraderivative also. Hence, one definition of gentian violet is practically the same as the other. It seems likely that in therapeutics it will be found that there is little difference between the penta and hexa derivatives and the mixtures of the two, so that the one most easily obtained in pure form (crystal violet) will be the one most used. The material which has been used by the workers so far, however, has been gentian violet.

Actions and Uses.—The use of gentian violet in therapeutics has recently been proposed by Churchman, who found that solutions of the dye had a selective action on certain bacteria and that the majority of gram-negative organisms survived exposure to gentian violet solutions in strengths far in excess of that required to kill gram-positive organisms; in fact, the action of the dye is sufficiently selective, so that often a "strain within a species" is not affected. Churchman's work, however, was done largely with a product containing dextrin as a diluent. Gentian violet is stated to possess properties of great penetration; to be bactericidal also bacteriostatic *in vivo* toward the selective organisms. Its chief application has been in the treatment of affections of the pleural cavity and of the joints, particularly in empyema and arthritis—affections in which staphylococci, *B. pyocyaneus* and *B. diphtheriae* are the causative agents. Young and Hill have also proposed the use of gentian violet intravenously in staphylococcus septicemia, chronic cystitis (from staphylococcus), osteomyelitis (with staphylococcus present). Intravenous injection of the dye in doses of 5 mg. per kilogram of body weight causes marked cyanosis, which persists for a few hours after injection, owing to the intense color of the dye. In feeble patients, cardiac stimulants should be given. Churchman also has found that acid fuchsin (the acid sodium salt of fuchsin disulphonic and trisulphonic acids) is in some respects the opposite of that of gentian violet in selective power, a stained culture of *B. prodigiosus* being killed by the acid fuchsin, while the gram-positive *B. anthracis* would be unaffected. The selective action of acid fuchsin, however, is clearly brought out only when the organisms are exposed to the dye with slight elevation of temperature (about 50 C.). Acid fuchsin is incompatible with gentian violet, and the compatibility of all mixtures of dyes should be determined before any combination is prepared. Churchman claims, however, that acriflavine possesses much the same selectivity as acid fuchsin, so he has proposed the use of a mixture of these two dyes. The effectiveness of such a solution has not yet been established clinically. None of the rosaniline dyes are strong bactericides.

GENTIAN VIOLET MEDICINAL.—A mixture of pentamethylpararosaniline and hexamethylpararosaniline chlorides.

Actions and Uses.—See preceding article, Triphenylmethane (Rosaniline) Dyes.

Dosage.—For direct application, a solution of from 1 in 500 to 1 in 1,000 may be employed; for instillation, a 1 in 10,000 solution. For intravenous use, Young and Hill recommend 5 mg. per kilogram of body weight, injected in 0.5 per cent dilution.

Gentian violet occurs as a dark green ("bronze") powder or greenish glistening pieces having a metallic luster. It is soluble in water (1 in 10), alcohol or chloroform; insoluble in ether. Its solution in alcohol or chloroform has a deeper hue than the same strength aqueous solution. Concentrated sulphuric acid dissolves methyl violet with an orange to brownish-red color; on slowly diluting this solution in distilled water, the solution assumes a brown, then green and finally a blue color.

Add, drop by drop, tannic acid solution to a solution of gentian violet (1 in 500): a deep blue precipitate forms (*basic color*). To 5 cc. of an aqueous solution of gentian violet, add a few drops of hydrochloric acid and about 0.5 Gm. of zinc dust: rapid decolorization ensues. Place a few drops of the decolorized solution near a few drops of ammonia water on filter paper: the zone of contact assumes a blue color.

Add hydrochloric acid slowly, drop by drop, with agitation to an aqueous solution of the dye (1 in 500); the violet color changes gradually to bluish-green, green and finally to brownish yellow, the solution remaining clear; now dilute gradually the solution: the color changes in reverse order as the hydrogen-ion concentration is increased.

Dissolve 1 Gm. of the dye in boiling alcohol; cool; filter through Gooch filter; wash residue with alcohol until washings cease to be colored violet and dry at 100 C.: the weight of insoluble material corresponds to not more than 1 per cent (*dextrin*).

When tested for arsenic according to the U. S. Pharmacopeia, X, the product should meet requirements for the test for arsenic (p. 428, Arsenic Test).

Incinerate 1 Gm. of gentian violet: not more than 0.01 Gm. of ash remains.

Gentian Violet Improved Medicinal.—A brand of gentian violet medicinal-N. N. R.

Manufactured by The Coleman and Bell Company, Norwood, Ohio. No U. S. patent or trademark.

Gentian Violet Medicinal-"National."—A brand of gentian violet medicinal-N. N. R.

Manufactured by The National Aniline and Chemical Company, New York. No U. S. patent or trademark.

Tablets Gentian Violet Medicinal-"National," 0.0324 Gm. (½ grain).

Enteric Coated Tablets Gentian Violet Medicinal-"National," 0.0324 Gm. (½ grain): The tablets are coated with phenyl salicylate containing some keratin.

EPHEDRINE

Ephedrine is an alkaloid first obtained by Nagai in 1887 from ma huang (*Ephedra equisetina*). Chemically, ephedrine is α-hydroxy-β-methylamino-propylbenzene ($C_6H_5.CHOH.CH(NHCH_3).CH_3.$). Structurally, it is closely related to epinephrine, and like epinephrine it is levorotatory; but it is more stable. Its salts are, in general, soluble in water and in alcohol.

Actions and Uses.—Ephedrine is reported to excite the sympathetic nervous system and to produce effects similar to those produced by epinephrine. It also has been found to exert a direct depressant action on smooth and cardiac muscle. It produces a rather lasting rise of blood pressure, on intravenous or intramuscular injection, due mainly to vasoconstriction. Other effects similar to those of epinephrine are dilatation of the bronchi and mydriasis after local or systemic administration. On local application, it contracts the capillaries to a moderate degree and thus reduces swelling of the turbinate bodies and diminishes hyperemia.

Thus far, the most definite indications for the usefulness of ephedrine are for its local use on the turbinates and for ophthalmic examinations. Ephedrine has proved effective in some cases of asthma, but in a considerable proportion of cases it has failed partially or completely; moreover, its oral administration generally causes symptoms of the anxiety complex, and this may constitute a definite contraindication to its use. Its use in serious heart disease is not yet considered safe. There is not as yet good evidence that ephedrine is of use in shock, hypotension and circulatory collapse and hemorrhage. It is without value in Addison's disease.

Dosage. Salts of ephedrine are quite effective whether given orally, intramuscularly, intravenously, or by any ordinary path of administration. As a spray it is used in 0.5 to 2 per cent solution of a salt of ephedrine; in ophthalmologic work it has been used in 4 per cent solution. Orally, the usual dose for adults is from 0.025 to 0.1 Gm. (½ to 2 grains).

EPHEDRINE.—Ephedrina.—Ephedrine base.—α-hydroxy-β-methyl-amino-propylbenzene ($C_6H_5.CHOH.CH[NHCH_3].CH_3.$). An alkaloid derived from *Ephedra equisetina.*

Actions and Uses.—The same as those of the ephedrine salts. The free alkaloid is employed in mediums, such as oils, in which it is more soluble than the salts.

Dosage.—One per cent, in oil, may be used for local application to mucous membranes.

Ephedrine occurs as an unctuous, almost colorless solid that tends to crystallize as needles. The needles melt at 34-40 C., and the liquefied alkaloid boils above 200 C. The specific rotation in absolute alcohol (Note: must be no moisture by anhydrous copper sulphate test) $[\alpha]\,\frac{D}{20}$ falls between —6 and —7.5. It is soluble in alcohol, chloroform, ether and water, the solutions being strongly alkaline to litmus paper moistened with water. Dissolve 0.0005 Gm. of ephedrine in 1 cc. of water and add 0.1 cc. of copper sulphate solution (10 per cent) followed by 1 cc. of sodium hydroxide solution (20 per cent): a reddish purple color develops. To this solution add 1 cc. of ether, shake the mixture and compare with a tube made up similarly, but without using ether: the reddish purple is partially extracted (apparently decolorized by the ether). Dissolve 0.05 Gm. of ephedrine in 10 cc. of choroform and allow to stand twelve hours, evaporate spontaneously: white crystals of ephedrine hydrochloride appear; wash with a little chloroform, dry: the crystals melt between 214 and 220 C.

Dissolve 0.05 Gm. of ephedrine in 30 to 40 cc. of distilled water, add 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution: less turbidity results than in a control tube using 0.1 cc. of fiftieth-normal hydrochloric acid (*limit of chloride*). Dissolve 0.05 Gm. of ephedrine in from 30 to 40 cc. of distilled water, add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution: no turbidity develops in ten minutes (*limit of sulphate*).

Dissolve about 0.2 Gm. of ephedrine, accurately weighed, in 10 cc. of ether in a previously tared beaker, add an excess of hydrogen chloride in ether, evaporate to dryness, dry to constant weight over calcium chloride, and weigh; dissolve the residue in distilled water and dilute with distilled water to 10 cc.; observe the angular rotation at 20 C.: the specific rotation in water $[\alpha]\,{}^{D}_{20}$ falls between —33 and —35.5.

Dissolve about 0.2 Gm., accurately weighed, in 10 cc. of neutralized alcohol, add 5 drops of bromcresol green solution and an excess of tenth-normal hydrochloric acid, titrate the excess, using fiftieth-normal sodium hydroxide solution: the acid used in neutralizing the ephedrine is equivalent to not less than 97 per cent, nor more than 100 per cent of the ephedrine used.

Place about 0.3 Gm. of ephedrine accurately weighed in a previously tared wide-mouthed weighing bottle in a desiccator and allow to stand over calcium chloride at room temperature for eighteen hours (the temperature should not go above 22 C.): it loses not more than 1.8 per cent of its weight.

Heat about 0.1 Gm. of ephedrine accurately weighed in a platinum dish until constant weight is obtained. The ash is less than 0.1 per cent.

Ephedrine-Lilly.—A brand of ephedrine-N. N. R.

Manufactured by Eli Lilly & Company, Indianapolis. No U. S. patent or trademark.

Inhalant Ephedrine Compound-Lilly: A solution containing ephedrine-Lilly, 1 per cent (by weight) in a liquid composed of menthol, 0.66 Gm.; camphor, 0.66 Gm.; oil of thyme, 0.31 cc.; liquid petrolatum to make 100 cc. U. S. patent applied for. No U. S. trademark.

Inhalant Ephedrine (Plain)-Lilly: A solution containing ephedrine-Lilly, 1 Gm.; cottonseed oil, 1 Gm.; perfumed with cinnamic aldehyde, benzaldehyde, and jasmine extract, and tinted with butter yellow; liquid petrolatum to make 100 cc. U. S. patent applied for. No U. S. trademark.

Ointment Ephedrine Compound: Ephedrine-Lilly, 1 Gm.; menthol, 0.65 Gm.; camphor, 0.65 Gm.; oil of thyme, 0.375 Gm.; hydrous wool fat, 5 Gm.; liquid petrolatum, 24 Gm.; white petrolatum to make 100 Gm.

Ephedrine-Swan-Myers.—A brand of ephedrine-N. N. R.

Manufactured by Swan-Myers Company, Indianapolis. No U. S. patent or trademark.

Ephedrine Inhalant-Swan-Myers: A 1 per cent solution of ephedrine-Swan-Myers in light liquid petrolatum tinted pink and perfumed with oil of rose. No U. S. patent or trademark.

EPHEDRINE HYDROCHLORIDE.—Ephedrinae Hydrochloridum.—*laevo*-methylaminopropanol benzene hydrochloride. —*alpha*-hydroxy-*beta*-methylamino-propylbenzene hydrochloride. — *1*-phenyl-*2*-methylamino-propan-*1*-ol hydrochloride. $C_6H_5.CHOH.CH(NHCH_3).CH_3.HCl$. The hydrochloride of an alkaloid obtained from *Ephedra equisetina.*

Actions and Uses.—See preceding article, Ephedrine.

Dosage.—See preceding article, Ephedrine.

Ephedrine hydrochloride occurs as white, odorless, crystals that are soluble in water and alcohol and insoluble in ether. The water solution is neutral to litmus. It melts between 216 C. and 220 C. The specific rotation $[a]\frac{20}{D}$ should fall between —33.0 and —35.50.

Dissolve 0.005 Gm. of ephedrine hydrochloride in 1 cc. of water and add 0.1 cc. of copper sulphate solution (10 per cent) followed by 1 cc. of sodium hydroxide solution (20 per cent): a reddish purple color develops. To this solution add 1 cc. of ether, shake the mixture and compare with a tube made up similarly but without using ether: the reddish purple color is partially extracted (apparently decolorized) by the ether.

Dissolve 0.05 Gm. of ephedrine hydrochloride in 10 cc. of water, add 1 cc. of ammonia water and shake out with two 15 cc. portions of chloroform, filter the chloroform through a chloroform soaked cotton pledget and allow to stand twelve hours, evaporate: white crystals of ephedrine hydrochloride appear; wash with a little chloroform, dry: the crystals melt between 214 and 220 C.

To 1 cc. of a solution containing 0.005 Gm. of ephedrine hydrochloride, add two drops of diluted nitric acid and two drops of silver nitrate solution: a white precipitate forms, soluble on addition of ammonia water in excess.

Dissolve 0.05 Gm. of ephedrine hydrochloride in from 30 to 40 cc. of distilled water, add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution. No turbidity develops in ten minutes (*limit of sulphate*).

Dissolve about 0.2 Gm. of ephedrine hydrochloride, accurately weighed, in 10 cc. of water in a separatory funnel and add 5 cc. of ammonia water; shake the mixture vigorously with 6 portions of ether, using 25 cc., 20 cc., 15 cc., 15 cc., 15 cc., and 15 cc., respectively; combine the ether extractions and distil to a small volume, then transfer to a beaker and evaporate spontaneously; dry in a desiccator for twelve hours; weigh: the weight of the residue is not less than 80 per cent, nor more than 82.5 per cent.

The specific rotation $[a]\frac{20}{D}$ of a residue obtained as described in the foregoing assay, weighing about 0.3 Gm. dissolved in absolute alcohol to make 10 cc. of solution is between —6.0 and —7.5 (*limit of isomers*).

Dissolve about 0.07 Gm. of ephedrine hydrochloride, accurately weighed, in 200 cc. of water, heat to boiling and add 4 cc. of diluted nitric acid and silver nitrate solution in slight excess; allow to stand for six hours, transfer to a Gooch crucible, wash well with hot water and then with cold, dry at 100 C., cool in a desiccator and weigh: the chloride (Cl^-) calculated from the silver chloride weighed is not less than 17.30 per cent nor more than 17.7 per cent.

The ash from 0.1 Gm. weighs less than 0.0001 Gm.

Ephedrine Hydrochloride-Abbott.—A brand of ephedrine hydrochloride-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

Capsules Ephedrine Hydrochloride-Abbott, 3/8 grain.

Capsules Ephedrine Hydrochloride-Abbott, 3/4 grain.

Ephedrine Hydrochloride Solution-Abbott, 3%: It is preserved with chlorbutanol, 0.5 per cent.

Tablets Ephedrine Hydrochloride-Abbott, 1/4 grain.

Tablet Triturates Ephedrine Hydrochloride-Abbott, 1/2 grain.

Ephedrine Hydrochloride-Lilly.—A brand of ephedrine hydrochloride-N. N. R.

Manufactured by Eli Lilly & Company, Indianapolis. No U. S. patent or trademark.

Hypodermic Tablets Ephedrine Hydrochloride-Lilly, 0.016 Gm. (¼ grain).

Hypodermic Tablets Ephedrine Hydrochloride-Lilly, 0.0325 Gm. (½ grain).

Pulvules Ephedrine Hydrochloride-Lilly, ⅜ grain.

Pulvules Ephedrine Hydrochloride-Lilly, ¾ grain.

Solution Ephedrine Hydrochloride-Lilly, 3%: It is preserved with chlorbutanol, 0.5 per cent.

Ephedrine Hydrochloride-Pemco.—A brand of ephedrine hydrochloride-N. N. R.

Capsules Ephedrine Hydrochloride-Pemco, ¼ grain.

Capsules Ephedrine Hydrochloride-Pemco, 0.3 Gm.: Each red capsule contains ephedrine hydrochloride-Pemco without diluent.

Prophylacto Manufacturing Co., Chicago, distributor. No U. S. patent or trademark.

Ephedrine Hydrochloride-Squibb.—A brand of ephedrine hydrochloride-N. N. R.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

Tablets Ephedrine Hydrochloride-Squibb, ⅜ grain.

Tablets Ephedrine Hydrochloride-Squibb, ¾ grain.

Ephedrine Hydrochloride-Swan-Myers.—A brand of ephedrine hydrochloride-N. N. R.

Manufactured by Swan-Myers Company, Indianapolis. No U. S. patent or trademark.

Ampoules Ephedrine Hydrochloride-Swan-Myers, 0.05 Gm., 1 cc.
Capsules Ephedrine Hydrochloride-Swan-Myers, 0.025 Gm.
Capsules Ephedrine Hydrochloride-Swan-Myers, 0.0324 Gm. (½ grain).
Capsules Ephedrine Hydrochloride-Swan-Myers, 0.05 Gm.
Solution Ephedrine Hydrochloride-Swan-Myers, 3%: It is preserved with chlorbutanol, 0.5 per cent.

Syrup Ephedrine Hydrochloride-Swan-Myers: Containing ephedrine hydrochloride-Swan-Myers, 0.2195 Gm., in 100 cc. (⅛ grain per fluidrachm) and alcohol 12 per cent.

Syrup Ephedrine Hydrochloride (Double Strength)-Swan-Myers: Containing ephedrine hydrochloride-Swan-Myers, 0.4390 Gm., in 100 cc. (¼ grain per fluidrachm) and alcohol 12 per cent.

EPHEDRINE SULPHATE.—Ephedrinae Sulphas.—*laevo*-methylaminopropanolbenzene sulphate. — *alpha*-hydroxy-*beta*-methylaminopropylbenzene sulphate.—*1*-phenyl-*2*-methylamino-propan-*1*-ol sulphate. $(C_6H_5.CHOH.CH(NHCH_3).CH_3)_2.H_2SO_4$. The sulphate of an alkaloid obtained from *Ephedra equisetina.*

Actions and Uses.—See preceding article, Ephedrine.

Dosage.—See preceding article, Ephedrine.

Ephedrine sulphate occurs in fine odorless white crystals. It is easily soluble in water and hot alcohol, but more difficultly soluble in cold alcohol. The water solution is neutral to litmus. The specific rotation [a] $\frac{20}{D}$ ranges from —29 to —30. It melts between 240 and 243C (corrected). Note: The rate of heating must be *strictly* according to the method of U. S. P. X.

Dissolve 0.005 Gm. of ephedrine sulphate in 1 cc. of water and add 0.1 cc. of copper sulphate solution (10 per cent), followed by 1 cc. of sodium hydroxide solution (20 per cent): a reddish purple color develops. To this solution add 1 cc. of ether, shake the mixture and compare with a tube made up similarly but without using ether: the reddish purple color is partially extracted (apparently decolorized) by the ether.

Dissolve 0.05 Gm. of ephedrine sulphate in 10 cc. of water, add 1 cc. of ammonia water and shake out with two 15 cc. portions of chloroform, filter the chloroform through a chloroform soaked cotton pledget and allow to stand twelve hours, evaporate: white crystals of ephedrine hydrochloride appear; wash with a little chloroform, dry: the crystals melt between 214 and 220 C.

To 1 cc. of a solution containing 0.005 Gm. of ephedrine sulphate, add 4 drops of diluted hydrochloric acid, followed by 1 drop of barium chloride solution: a white precipitate forms.

Dissolve 0.05 Gm. of ephedrine sulphate in 30 to 40 cc. of distilled water, add 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution: less turbidity results than in a control tube using 1 cc. of fiftieth normal hydrochloric acid (*limit of chloride*).

Transfer about 0.2 Gm. of ephedrine sulphate accurately weighed to a separatory funnel, and add 10 cc. of water and 5 cc. of ammonia water, shake the mixture vigorously with 6 portions of ether, using 25 cc., 20 cc., 15 cc., 15 cc., 15 cc. and 15 cc., respectively; transfer the combined ether fractions to a distillation apparatus, distil to a small bulk, transfer to a tared beaker, rinse the distillation flask with a small amount of ether, then evaporate spontaneously; dry in a desiccator for twelve hours, weigh: the weight of ephedrine should not be less than 74.5 per cent, nor more than 77.25 per cent.

The specific rotation [a] $\frac{20}{D}$ of a residue obtained as described in the determination of ephedrine, weighing about 0.3 Gm. dissolved in absolute alcohol to make 10 cc. of solution is between —6.0 and —7.5 (*limit of isomers*).

Dissolve about 0.05 Gm. of ephedrine sulphate, accurately weighed in 200 cc. of water, add 1 cc. of diluted hydrochloric acid, followed by sufficient barium chloride solution to precipitate all the sulphate, allow to stand for one hour, transfer the precipitate to a previously prepared Gooch crucible, wash well with hot water and then with cold water, dry at 120 C., cool in a desiccator, weigh: the sulphate (SO_4^{--}) calculated from the barium sulphate weighed is not less than 21.80 per cent, nor more than 23.10 per cent.

The ash from 0.1 Gm. weighs less than 0.0001 Gm.

Ephedrine Sulphate-Abbott.—A brand of ephedrine sulphate-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

Ephedrine Sulphate-Lilly.—A brand of ephedrine sulphate-N. N. R.

Manufactured by Eli Lilly & Company, Indianapolis. No U. S. patent or trademark.

Hypodermic Tablets Ephedrine Sulphate-Lilly, 0.016 Gm. (¼ grain).

Hypodermic Tablets Ephedrine Sulphate-Lilly, 0.0325 Gm. (½ grain).

Lilly's Ephedrine Jelly: Ephedrine sulphate-Lilly, 1 Gm.; glycerin, 15 Gm.; tragacanth, 1.5 Gm.; eucalyptol, 0.1 Gm.; oil of wintergreen, 0.005 Gm.; oil of dwarf pine needles, 0.005 Gm., water to make 100 Gm.

Pulvules Ephedrine Sulphate-Lilly, 0.025 Gm.: Each pulvule (filled capsule) contains ephedrine sulphate-Lilly, 0.025 Gm. (⅜ grain).

Pulvules Ephedrine Sulphate-Lilly, 0.05 Gm.: Each pulvule (filled capsule) contains ephedrine sulphate-Lilly, 0.05 Gm. (¾ grain).

Ampoules Ephedrine Sulphate-Lilly, 1 cc., 0.05 Gm.: Each ampoule contains ephedrine sulphate-Lilly, 0.05 Gm. (¾ grain) in 1 cc. of solution.

Solution Ephedrine Sulphate-Lilly, 3 per cent: It is preserved with chlorbutanol, 0.5 per cent.

Syrup No. 110 Ephedrine Sulphate: Containing ephedrine sulphate-Lilly, 0.22 Gm., in 100 cc. (1 grain per fluidounce) and alcohol 12 per cent; it is flavored with vanillin, benzaldehyde and tolu, and tinted with amaranth.

Syrup No. 111 Ephedrine Sulphate: Containing ephedrine sulphate-Lilly, 0.44 Gm., in 100 cc. (2 grains per fluidounce) and alcohol, 12 per cent; it is flavored with vanillin, benzaldehyde and tolu, and tinted with amaranth.

Ephedrine Sulphate-P. D. & Co.—A brand of ephedrine sulphate-N. N. R.

Manufactured by Parke, Davis & Company, Detroit. No U. S. patent or trademark.

Capsules Ephedrine Sulphate-P. D. & Co., 0.025 Gm. (⅜ grain).

Capsules Ephedrine Sulphate-P. D. & Co., 0.05 Gm. (¾ grain).

Glaseptic Ampoules Ephedrine Sulphate-P. D. & Co., 0.05 Gm. (¾ grain), 1 cc.

Solution Ephedrine Sulphate-P. D. & Co., 3 per cent: It is preserved with chlorbutanol, 0.5 per cent.

EPINEPHRINE AND EPINEPHRINE PREPARATIONS

Epinephrine, the active principle of the suprarenal glands, is extensively used in surgery and to a less extent in medicine in the form of the 1 in 1,000 solution of epinephrine hydrochloride (solution of epinephrine hydrochloride, U. S. P.). The alkaloid, in addition to being obtained from the suprarenal glands, is also prepared synthetically; and such preparations, if they are levorotatory, are equally as active as the natural product. Artificial epinephrines have also been prepared which are optically inactive, and such are only about half as active physiologically as is natural epinephrine. Dextrorotatory epinephrine is still weaker. The levorotatory product is the only one used in medicine.

EPINEPHRINE.—For description see the U. S. Pharmacopeia and Useful Drugs under Epinephrina.

Actions and Uses.—Epinephrine acts peripherally on a variety of structures by stimulating the myoneural junctions of the sympathetic nerve endings when it is given intravenously. Its most important actions consist of a constriction of the blood vessels with consequent rise of blood pressure; a stimulation of the vagus center causing slowing of the heart; and a direct stimulant effect on the heart muscle, similar to that of digitalis. Large doses also cause glycosuria. The effect of a single intravenous dose is fleeting. It is not irritant. These effects are best seen on intravenous and intramuscular injection. When given to animals, by mouth or hypodermically, moderate doses have practically no action.

Dilute watery solutions rapidly lose their strength, the deterioration being accompanied by a reddish or brownish discoloration.

Epinephrine is chiefly used locally for its vasoconstrictor action in hemorrhage, and in catarrhal and congestive conditions. It often relieves asthmatic paroxysms when used by hypodermic injection. Intravenous injections are sometimes effective in shock and anesthesia accidents (care being taken not to give an overdose). It has also been recommended in Addison's disease, but opinions are divided as to the benefits to be expected from its use.

The vasoconstrictor action of epinephrine is used to prolong the anesthetic effect of local anesthetics by retarding the circulation in the injected area and thus hindering the dilution of the anesthetic agent by too rapid absorption into the blood stream.

Dosage.—Hypodermically or intramuscularly from 0.06 to 1 cc. (1 to 15 minims) of a 1 in 1,000 solution, diluted with sterile salt solution. Locally, it is used in solution varying in strength from 1 in 15,000 to 1 in 1,000. It is also used in oily solution for sprays, in ointment for application to mucous membranes, such as the eye or the nose, where a slower but more lasting action is desired, and in suppositories.

Adrenalin.—A brand of epinephrine-U. S. P. Made from the suprarenal gland.

Manufactured by Parke, Davis & Company, Detroit, Mich. U. S. patent 730,175, 730,176, 730,196, 730,197, 730,198 (June 2, 1903; expired); 753,177 (Feb. 23, 1904; expired). U. S. trademark 53,934.

Adrenalin Chloride Solution: A solution containing 1 part of adrenalin chloride in 1,000 parts of physiologic salt solution, preserved by the addition of 0.5 per cent of chloretone.

Adrenalin Inhalant: A neutral oily solution containing adrenalin chloride 1 in 1,000, 3 per cent of chloretone, 15 per cent of alcohol, and aromatics.

Adrenalin Ointment: One part of adrenalin chloride in 1,000 parts of oleaginous ointment base.

Adrenalin and Chloretone Ointment: One tenth per cent of adrenalin chloride, and 5 per cent of chloretone in an ointment base of hydrous wool fat and petrolatum.

Adrenalin Suppositories: One part of adrenalin chloride to 1,000 parts of oil of theobroma (cacao butter). Each suppository weighs about 1 Gm. (15 grains).

Adrenalin Tablets: One thousandth Gm. (3/200 grain) adrenalin, as borate, yielding a 1 in 1,000 solution when dissolved in 15 minims (1 cc.) of water.

Adrenalin Tablets No. 2: Each contains adrenalin, 0.00033 Gm. (1/200 grain) as borate, yielding a 1 in 1,000 solution when dissolved in 5 minims of water.

Adrenalin and Cocaine Tablets: Each hypodermic tablet contains cocaine hydrochloride 0.01 Gm. (1/6 grain), and adrenalin 0.00005 Gm. (1/1800 grain).

Ampoules Adrenalin Chloride Solution ℞ 1, 1:10,000, 1 cc.: a solution of adrenalin chloride 1 part, in physiological solution of sodium chloride 10,000 parts, without preservative.

Ampoules Adrenalin Chloride Solution ℞ *2, 1:2,600, 1 cc.:* a solution of adrenalin chloride 1 part, in physiological solution of sodium chloride 2,600 parts, without presrvative.

Ampoules Adrenalin Chloride Solution 1:1,000, 1 cc.: a solution of adrenalin chloride 1 part, in physiological solution of sodium chloride 1,000 parts, without preservative.

Suprarenalin.—A brand of epinephrine-U. S. P. Made from the suprarenal gland.

Manufactured by Armour & Co., Chicago. U. S. patent 829,220 (Aug. 21, 1906; expired). No U. S. trademark.

Suprarenalin: vials containing suprarenalin, 1 grain.

Suprarenalin Ointment: one part of suprarenalin suspended in 1,000 parts of petrolatum base.

Suprarenalin Solution: a solution containing suprarenalin sulphite equivalent to 1 part of suprarenalin in 1,000 parts of physiological solution of sodium chloride without addition of other preservatives.

L-SUPRARENIN SYNTHETIC BITARTRATE.—The acid tartrate of synthetic epinephrine obtained by the method of Stolz and Flaecher (*Ztschr. f. physiol. Chem.* **58**:189).

Actions, Uses and Dosage.—See Epinephrine. Synthetic epinephrine has the physiologic effects of natural epinephrine obtained from suprarenal gland.

Manufactured by H. A. Metz Laboratories, Inc., New York. U. S. patent 986,156 (March 7, 1911; expires 1928).

L-Suprarenin Synthetic Bitartrate Tablets, 0.001 Gm.: L-suprarenin synthetic bitartrate, equivalent to 0.001 Gm. (1/65 grain) synthetic epinephrine (free base).

Synthetic epinephrine (the free base) is a white odorless powder nearly insoluble in water, alcohol and ether. It melts at from 211 to 212 C. It rotates polarized light to the left, the rotation being

$$[a]\,\frac{19.6^\circ}{D} = -\,51.4^\circ$$

It has the chemical and physical properties of epinephrine obtained from suprarenal glands.

L-suprarenin synthetic bitartrate is a white odorless powder soluble in water and yielding a solution which has an acid reaction. L-suprarenin synthetic bitartrate melts at 149 C. and its aqueous solution rotates polarized light to the left.

TYRAMINE HYDROCHLORIDE.—**Tyraminae Hydrochloridum.**—Tyramine.—*p*-hydroxyphenylethylamine hydrochloride.—$OH.C_6H_4CH_2CH_2NH_2.HCl$.—The hydrochloride of the base *p*-hydroxyphenylethylamine $OH.C_6H_4.CH_2.CH_2.NH_2$ obtained synthetically.

Actions and Uses.—The actions of tyramine hydrochloride resemble those of epinephrine; they are less powerful but more persistent. It is absorbed much more readily.

Tyramine hydrochloride produces a rise of blood pressure, mainly by vasoconstriction. This suggested its employment in shock or collapse, but it has not been very successful. It is useless as a local hemostatic.

Tyramine hydrochloride seems to have a possible field in obstetrics, since it contracts the uterus and thus checks postpartum hemorrhage; but it is not so powerful as pituitary extract. It is also useful in that it antagonizes the respiratory depression of morphine, thus rendering this drug safer in childbirth.

Dosage.—Tyramine hydrochloride acts fairly well from the stomach, but is best given hypodermically, in doses of from 0.02 to 0.04 Gm. (⅓ to ⅔ grain), dissolved in water.

The base parahydroxyphenylethylamine was isolated from ergot by Barger and also prepared synthetically by him by the reduction of parahydroxyacetonitrile with sodium in alcoholic solution (Transactions of the Chemical Society, 1909, xcv). It had previously been obtained by heating tyrosine; hence its name. It is chemically and physiologically related to epinephrine.

Tyramine hydrochloride occurs as a white, or almost white, crystalline powder, soluble in water and forming a neutral solution.

On careful addition of a few drops of sodium hydroxide solution to a solution of tyramine hydrochloride, a crystalline precipitate of parahydroxyphenylethylamine is produced. Millon's reagent added to a solution of tyramine hydrochloride produces a red precipitate or a red color. If an alkaline solution of tyramine is treated with benzoyl chloride, a dibenzoyl derivative is obtained which melts at 169 C.

A 1 in 10,000 solution of tyramine hydrochloride produces a distinct contraction in the surviving intestine of the guinea-pig, while doses of from 0.001 to 0.005 Gm. produce measureable increase in the blood pressure of the rabbit.

Tyramine-Roche.—A brand of tyramine hydrochloride-N. N. R.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J.). No U. S. patent or trademark.

ERGOT

It has been shown that ergot contains alkaloids which are specific for ergot, and a number of amines. These amines, however, are decomposition products of proteins and probably do not exist in fresh ergot.

The chief constituents are:

1. Ergotoxine or hydroergotinine, $C_{35}H_{41}O_6N_5$, an amorphous alkaloid occurring in alcoholic extracts. It causes the characteristic reaction of ergot on the cock's comb, and is concerned in the uterine and vascular effects. It is rather unstable and by loss of water changes into its anhydride, crystalline ergotinine, $C_{33}H_{39}O_5N_5$, which possibly because of its low solubility in physiological solutions is quite weak in action. This pair of alkaloids, the amorphous and the crystalline ergotinine, exist already formed in ergot, and each member can easily be converted into the other by chemical means. Both are insoluble in water and petroleum benzin, sparingly soluble in ether, and readily soluble in almost all other organic solvents. Amorphous ergotinine or ergotoxine is easily soluble in cold alcohol; crystalline ergotinine is sparingly soluble. They dissolve in dilute sodium hydroxide; but the latter alkaloid is partially converted into ergotoxine. Their salts form colloidal solutions with water, but these are precipitated by electrolytes (salts or mineral acids).

2. (a) Ergotamine, $C_{33}H_{35}N_5O_5$, a crystalline alkaloid. Ergotamine causes contraction of the uterus of the guinea-pig, rat, cat, and of the human subject and increases the blood pressure through action on the motor endings of the sympathetic division of the autonomic nervous system. In sufficient dosage it causes darkening of the cock's comb (characteristic of the action of ergot), and with toxic doses convulsions and development of gangrene of the cock's comb or of the tail of the white rat.

Ergotamine is insoluble in water, easily soluble in methyl and ethyl alcohol, acetone, and chloroform, less so in ether. It forms water-soluble salts. Ergotamine and its salts crystallize easily. It is unstable by its sensitiveness to heat, light, and air. By chemical means it is easily changed into

(b) Ergotaminine. This is a crystalline isomer of ergotamine. It is very little soluble in ethyl alcohol and other organic solvents, much less so than ergotamine and ergotoxine. It is strongly dextro-rotatory, while ergotamine is laevo-rotatory in chloroform. Ergotaminine is less active than ergotamine.

3. ρ-hydroxyphenylethylamine, $OH.C_6H_4.CH_2.CH_2NH_2$, or tyramine. This is closely related to epinephrine in structure and action. It is mainly responsible for the pressor effect, and is not materially concerned in the uterine action.

4. β-iminazolylethylamine, 4-*m*-aminoethylglyoxaline, $C_3H_3.N_2CH_2.CH_2.NH_2$, or histamine. This lowers the blood pressure in carnivores and stimulates the *excised* uterus powerfully.

A number of other aromatic amines occur, such as agmatine, guanidobutylamine and isoamylamine. Acetylcholine is frequently present, and lowers the blood pressure both by vasodilatation and by cardiac inhibition.

These aromatic amines are not specific for ergot, being produced by putrefaction in extracts of both animal and plant origin. They are derived from the amino-acids by the splitting off of carbon dioxide: tyramine from tyrosine; histamine from histidine; agmatine from arginine; isoamylamine from leucine. It is not known whether they are present in fresh ergot or not; but they have been shown not to be present in fresh rye.

Ergotin is a term applied to a variety of pharmaceutical extracts, generally prepared in such a way that they contain mainly the amines, and relatively small amounts of the alkaloids.

It will be seen that there are a number of the constituents of ergot which exert some effect upon the excised uterus, but only the alkaloids have a prolonged effect upon the human uterus when used clinically. The action of the amines is chiefly that of histamine, and such evidence as is available indicates that the action of this substance is transitory.

Moreover histamine and tyramine require massive doses to produce their circulatory effects when given by mouth, and in the absence of positive evidence it is to be questioned whether any of the uterine effects which follow the oral administration of active ergot preparations are to be ascribed to the relatively small amounts of amines present.

The galenic preparations must vary in composition according to the solvent. The alcoholic fluid extract contains both the alkaloids and the amines; the aqueous preparations, including the solid extracts and "ergotins," contain chiefly if not solely the non-specific amines.

All ergot preparations, especially those containing water, deteriorate with age. It is necessary therefore to standardize them, and the date of assay should be indicated on the container. No satisfactory chemical method of standardization is available, and it is therefore necessary to use biological methods. A number of different methods have been proposed, but if the current belief is confirmed that the activity of ergot as used clinically is due chiefly if not solely to the alkaloids present, then a method of assay should be used which is a measure of the alkaloidal content. In this country the cock's comb method (official in the U. S. P. X) is commonly employed for this purpose.

ERGOT ASEPTIC.—A liquid extract of ergot, standardized by the cock's comb method of assay to have the same potency as fluidextract of ergot-U. S. P.

Actions and Uses.—The same as those of ergot.

Dosage.—1 to 2 cc. Ergot aseptic is intended for intramuscular injection. Ergot aseptic is marketed in ampules only. The date of manufacture appears on each package and the product is not guaranteed to possess its full potency for more than one year from time of manufacture.

Manufactured by Parke, Davis and Co., Detroit. No U. S. patent or trademark.

Ampoules Ergot Aseptic 1 cc.

Ergot is extracted with diluted alcohol acidulated with hydrochloric acid. The percolate is partially neutralized with alkali and concentrated by distillation in a partial vacuum at a temperature not above 80 C. A large excess of alcohol is added to the concentrated percolate and the material which precipitates is removed. The liquid portion is freed from alcohol by distillation in a partial vacuum at a low temperature, and chlorbutanol in the proportion of 0.005 Gm. per cc. added to the aqueous slightly acid liquid. After three weeks the liquid is assayed, adjusted to proper volume and sealed in ampules. The finished ampules are tested for sterility and potency.

Ergot aseptic is standardized to the same potency as fluidextract of ergot-U. S. P., as determined by the cock's comb method described in the U. S. P. X.

GYNERGEN.—Ergotamine Tartrate.—$(C_{33}H_{35}O_5N_5)_2.H_2C_4H_4O_6$.—The normal tartrate of the principal alkaloid of ergot, $C_{33}H_{35}O_5N_5$.

Actions and Uses.—Gynergen stimulates the motor nerve endings of the sympathetic division of the autonomic nervous system, thus causing an increase in blood pressure, contraction of the uterus, etc. (the isolated uterus of the guinea-pig is affected in dilution of from 1 in 150,000,000 to 1 in 200,000,000). In large doses it paralyzes the sympathetic nerve endings and causes the darkening of the cock's comb characteristic of the action of ergot. In toxic doses it causes gangrene and convulsions.

Gynergen is proposed for use when the action of ergot to produce uterine contraction is desired; it is contraindicated whenever tonic contraction of the uterus is undesirable. Gynergen is also stated to be indicated in hemorrhage following abortion, after curettage and in postpartum endometritis. It is also used in conditions in which there is believed to be overactivity of the sympathetic nervous system, as in Graves' disease.

Dosage.—Intramuscularly, the average dose is 0.25 mg.; orally, 1 mg. two to four times daily.

Manufactured by Sandoz Chemical Works, Basel, Switzerland (Sandoz Chemical Works, Inc., New York, distributor). U. S. patent 1,394,233 (Oct. 18, 1921; expires 1938); 1,435,187 (Nov. 14, 1922; expires 1939). U. S. trademark 173,047.

Ampules Gynergen, 1 cc.: Each cubic centimeter of solution contains **0.0005 Gm. of gynergen and a small excess of tartaric acid.**

Tablets Gynergen, 0.001 Gm.

Ergotamine tartrate ordinarily crystallizes with solvents of crystallization. Ergotamine tartrate with ethyl alcohol of crystallization occurs as colorless rhombic crystals that are difficultly soluble in water; these crystals lose their solvent of crystallization (sometimes as much as 8 per cent) in a high vacuum beginning at ordinary temperature and raising the temperature to 105 C.

Ergotamine tartrate is soluble in water (1 in 500) and in ethyl alcohol (1 in 500); on heating it blackens at 177 C., and at 184 C. it decomposes with the evolution of gas. Dissolve about 0.001 Gm. of ergotamine tartrate in a mixture of 5 cc. of glacial acetic acid and 5 cc. of ethyl acetate; to 1 cc. of this solution add slowly and with continual agitation and cooling 1 cc. of sulphuric acid: a blue color with a red tinge develops; add 0.1 cc. of diluted ferric chloride (1 in 1); the red tinge becomes less pronounced and the blue color more pronounced. Add 0.1 cc. of potassium mercuric iodide solution to 2 cc. of a solution of ergotamine tartrate (1 in 50,000): a slight turbidity appears. Add 0.1 cc. of trinitrophenol solution to 2 cc. of a solution containing ergotamine tartrate (1 in 20,000): a turbidity appears. In a subdued light, transfer 0.5 Gm. of ergotamine tartrate to a separatory funnel containing 20 cc. of water and 1 cc. of ammonia water, shake the solution with three portions of chloroform (20 cc., 15 cc. and 15 cc.), combine the chloroform extracts and evaporate spontaneously; transfer a weighed portion to a beaker, add 10 times the weight of acetone at 30 C.; if the solid does not dissolve mark the height of the liquid in the beaker and then add twice the volume of acetone already present and warm; if the solid still does not dissolve, filter, reject the residue and evaporate the filtrate to the volume already marked; add 0.7 part of water and cool to 0 C. for two hours, filter off the crystals and wash with 2 cc. of ether: the crystals are rhombic and are highly refractive. Dry the crystals for twenty-four hours in a high vacuum: the crystals lose their solvent of crystallization, and become a lusterless powder that has the following properties: on heating, the powder blackens at 174 C. and decomposes with the evolution of gas at from 181 to 182 C. It is very soluble in chloroform and glacial acetic acid, but is less soluble in alcohol, benzene and ether. The specific rotation $[a]\frac{20}{D}$ of a 0.6 per cent solution in chloroform is between —125 and —155.

TYRAMINE HYDROCHLORIDE.—See Epinephrine and Epinephrine Preparations.

ERIODICTYON.—For description see the U. S. Pharmacopeia under Eriodictyon.

Malto-Yerbine: A liquid containing in each hundred cc. an extract of 6.6 Gm. (30 grains per fluidounce) of eriodictyon (yerba santa), also flavoring composed of the essential oils of anise, cassia, coriander and caraway in maltine (which see under extract of malt) as a vehicle.

Manufactured by The Maltine Company, Brooklyn. No U. S. patent. U. S. trademark 44,566.

The extract of yerba santa employed in malto-yerbine is prepared as follows:

The leaves of yerba santa in coarse powder are boiled under pressure for six hours and inert matter separated by a filter process. The filtrate is concentrated with a certain quantity of maltine at a high temperature until the product has reached a density of 1.35. This extract is mixed in proper proportions with maltine of extra diastasic strength to make up for the diastasic strength lost through heat during the concentration of the drug with maltine.

Weigh a quantity of arrowroot starch, equivalent to 5 Gm. of anhydrous starch, boil it for ten minutes with 300 cc. of water and cool the mixture to 40 C. Add 25 cc. of a 4 per cent solution of maltine (equivalent to 1 Gm. of maltine) previously brought to a temperature of 40 C., and mix thoroughly.

Maintain the temperature at 40 C. for exactly 30 minutes. Add 6 cc. of sodium hydroxide test solution and mix. Add 5 drops of this solution to 5 cc. of a very dilute iodine solution (1 cc. of iodine solution in 100 cc. of water). A blue or red color does not appear.

ETHYLHYDROCUPREINE

Ethylhydrocupreine is a synthetic derivative of cupreine, $C_{10}H_{22}O_2N_2$, an alkaloid occurring together with quinine in the bark of *Remijia pedunculata.* It is closely related to quinine, differing from the latter in containing two more hydrogen atoms and an ethoxy group in place of a methoxy group. Ethylhydrocupreine has the antimalarial and anesthetic action of quinine. Toxic symptoms, however, such as tinnitus, deafness, amblyopia or amaurosis (retinitis) are more liable to occur than with quinine. While these are generally transient, retinitis may result in permanent impairment of vision (in one case, amaurosis resulted from the administration of two 0.25 Gm. doses of the hydrochloride). This demands caution in the administration of the drug. Ethylhydrocupreine has a specific bactericidal effect on the pneumococcus in vitro and it exerts a protective and curative action in animals experimentally infected with virulent strains of pneumococci. Clinical investigation indicates that the drug may be of value in the treatment of lobar pneumonia, if a sufficient amount can be administered sufficiently early without untoward effect. To avoid such effect, it is proposed to secure slow absorption through the administration of the free base by mouth. The hydrochloride may be administered intramuscularly, but it is liable to be irritant. Intravenous administration seems to be contraindicated. The drug has a definite value in the treatment of pneumococcic infections of the eye (ulcus corneae serpens).

OPTOCHIN BASE. — Optochin. — Ethylhydrocupreine.— $C_{10}H_{22}N_2OH.OC_2H_5$.

Actions and Uses.—See preceding article, Ethylhydrocupreine.

Dosage.—Optochin base is administered orally in doses of 0.25 Gm. (4 grains) every five hours for three days, each dose being accompanied by 150 cc. (5 fluidounces) of milk to retard absorption. If auditory or visual disturbances develop, the use of the drug is to be suspended. For children a proportionate dose is administered.

Manufactured by Merck & Co., Inc., Rahway, N. J., under U. S. patent 1,062,203 (May 20, 1913; expires 1930) by license of the Chemical Foundation, Inc. U. S. trademark 99822.

Tablets Optochin Base, 2 grains.

Optochin base is a white or faintly yellowish amorphous odorless powder, having a bitter taste. It is almost insoluble in water, soluble in alcohol, ether, chloroform, and in diluted mineral acids; slightly soluble in petroleum benzin.

Dissolve about 0.1 Gm. of optochin base in 20 cc. of water by the aid of a few drops of diluted sulphuric acid; add 1 cc. of bromine water and make the solution alkaline with ammonia water: a green color is produced. Dissolve about 0.5 Gm. of optochin base in water by means of a few drops of diluted sulphuric acid; render the solution alkaline by addition of sodium hydroxide solution and boil the mixture: no odor of ammonia develops. Dissolve about 0.1 Gm. of optochin base in 20 cc. of water by the aid of a few drops of diluted sulphuric acid: a blue, fluorescent solution is produced. Add 0.3 cc. of tenth-normal potassium permanganate solution to this solution: the violet color persists for at least one minute (*quinine and some other impurities*). Dissolve about 0.01 Gm. of optochin base in 0.2 cc. of sulphuric acid, U. S. P.: not more than a slightly greenish-yellow color is produced (*readily carbonizable organic impurities*).

Incinerate from 0.8 to 1 Gm. of optochin base, weighed accurately; not more than 0.1 per cent of ash remains.

OPTOCHIN HYDROCHLORIDE. — $C_{10}H_{22}N_2OH.O.C_2H_5HCl$.—The hydrochloride of ethylhydrocupreine.

Actions and Uses.—See preceding article, Ethylhydrocupreine.

Dosage.—For application to the eye and instillation into the conjunctival sac, a freshly prepared 1 or 2 per cent solution is used. It is not recommended for oral administration.

Manufactured by Merck & Co., Inc., Rahway, N. J., under U. S. patent 1,062,203 (May 20, 1913; expires 1930) by license of the Chemical Foundation, Inc. U. S. trademark 99822.

Optochin hydrochloride is a white or faintly yellowish-white crystalline, odorless powder, having a very bitter taste. It is soluble in 2 parts of warm water, forming a neutral or faintly alkaline solution; soluble in 5 parts of alcohol; very soluble in chloroform; almost insoluble in ether or petroleum benzin.

To 5 cc. of an aqueous solution of optochin hydrochloride (1 in 10) add 1 cc. of silver nitrate solution: a white, curdy precipitate is formed which is insoluble in nitric acid. To 5 cc. of an aqueous solution of optochin hydrochloride (1 in 10) add an excess of sodium hydroxide solution: a white curdy precipitate is produced (*distinction from cupreine, which is soluble in an excess of sodium hydroxide*). Dissolve about 0.1 Gm. optochin hydrochloride in 20 cc. of water and add 0.3 cc. tenth-normal potassium permanganate: the violet color persists for at least 1 minute (*quinine salts and some other impurities*). Dissolve about 0.01 Gm. of optochin hydrochloride in 0.2 cc. of sulphuric acid, U. S. P.: not more than a slightly greenish-yellow color is produced (*readily carbonizable organic impurities*).

Accurately weigh from 0.5 to 0.8 Gm. of optochin hydrochloride; dissolve it in about 20 cc. of water in a separator made slightly alkaline with ammonia water and extract the mixture successively with 15, 10 and 5 cc. of chloroform; allow the extractions to evaporate spontaneously; treat the residue with 2 cc. of alcohol; allow the alcohol to evaporate and dry the residue to constant weight at 100 C.: the weight of the residue (ethyl-hydrocupreine) corresponds to not less than 90 per cent of the weight of material taken for the assay.

FIBRIN FERMENTS AND THROMBOPLASTIC SUBSTANCES

The clotting of blood (that is, the transformation of the fibrinogen of circulating blood into the insoluble fibrin of blood clot) has been shown to be due to the action of the fibrin ferment (thrombin) on the fibrinogen of the blood. The fibrin ferment of thrombin exists in the blood in the form of its forerunner (prothrombin) which is acted on by the calcium salts and converted into thrombin. Besides calcium salts, however, another factor is necessary. In spite of a sufficient supply of calcium salts, blood does not clot spontaneously within the vessels. This other factor may be furnished by the breaking down of blood cells or blood platelets or by the pieces of tissues that are cut or badly injured. It has been designated as "zymoplastic" substance by Schmidt, as "thrombokinase" by Morowitz, and as "thromboplastic substance" or "thromboplastin" by Howell. Howell believes that the reason why blood does not coagulate within the vessels is that the prothrombin exists there in combination with an inhibiting substance which prevents it from acting. He believes that when blood is shed or flows over injured tissue the thromboplastin derived from blood cells, blood platelets or tissue cells combines with, or neutralizes, this inhibiting substance, liberating the prothrombin from combination with the latter. The prothrombin thus liberated and activated by the calcium salts, is converted into thrombin and converts the fibrinogen of the plasma into fibrin, causing coagulation to set in. Howell has shown that thromboplastin or "thromboplastic substance," from every source in which he has investigated it, contains the phosphatid cephalin (also written kephalin), and that the facilitating influence of thromboplastin on coagulation is due to the action of the cephalin. It is soluble in ether, but insoluble in alcohol and acetone. In solution or in solid form, cephalin gradually loses its power to hasten the clotting of blood, owing probably to an oxidation of the unsaturated fatty acids in the molecule.

Actions and Uses.—Preparations containing thromboplastin are said to be useful when applied locally in the treatment of hemorrhages, especially hemorrhages from oozing surfaces; likewise in the treatment of scar tissues, in nose bleed, and in surgery of the bones, glands, nose and throat. When injected subcutaneously or intravenously, such preparations are said to shorten the coagulation time of the blood for a period of about twenty-four hours, but there may be a certain danger of a negative phase setting in. Such injections are contraindicated in cases in which there is a tendency to thrombosis or embolism: for example, in arteriosclerosis, aneurysm, heart weakness, phlebitis, certain stages of syphilis, and in varicose veins. Injections of cephalin seem to have little effect in hemophilia (Hurwitz, S. H., and Lucas, W. P.: *Arch. Int. Med.* **17**:543 [April] 1916). Preparations should be standardized by testing on specimens of blood *in vitro*, which should be able to bring the coagulation time to about one third of its original length; they should be proved to be sterile, particularly if intended for intravenous use.

BRAIN LIPOID.—Impure Cephalin.—Impure Kephalin.—An ether extract of the brain of the ox, or other mammal, prepared according to the method of Howell as applied in practice by Hirschfelder (*Lancet* **2**:542, 1915) and described below.

Actions and Uses.—See preceding article, Fibrin Ferments and Thromboplastic Substances.

Dosage.—Brain lipoid may be spread on gauze sponges, pledgets, or on the tissues themselves; or an emulsion may be prepared by shaking up with physiological solution of sodium chloride and used in the same way or sponged over the tissues.

For use in an office or dispensary, the ether extract suffices and can be kept ready for use for some time (several months) in a sterile dropper bottle from which an opalescent emulsion can be prepared at a moment's notice by dropping from 10 to 30 drops into an ounce of physiological solution of sodium chloride and then shaking. This solution can also be dispensed from drug stores, provided the opening in the stopper of the dropper bottle is kept slightly open to prevent the ether's blowing off when the bottle is shaken or heated.

Brain lipoid (impure cephalin) is prepared from ox brain which is run through a hashing machine, then covered with 3 volumes of alcohol and agitated two or three times. The excess of alcohol is then poured off and squeezed out gently through linen, care being taken to avoid great force in wringing out the alcohol, as this tends to break up the brain tissue into very finely divided particles which pass through the filter. The residue is then covered with 3 volumes of ether, shaken vigorously and filtered first through cotton and then through filter paper. The clear filtrate thus obtained is evaporated to dryness over a water bath, leaving a yellow residue of fatty appearance and consistency. (This residue consists largely of cephalin, but though the latter is not in the pure state, it is extremely active in accelerating the clotting of blood *in vitro*.)

The method of preparation renders it sterile. It can be transferred on a sterile spatula or knife blade to sterile vessels. It retains its activities for several weeks.

(The impurities, largely the lecithins and myleins, do not materially interfere with the activity of the cephalin, but, on the contrary, facilitate its emulsification in physiological solution of sodium chloride and thus facilitate its intimate miscibility with blood.)

Kephalin-Armour.—The hemostatic phosphatid obtained from the brain tissue of cattle. It is essentially the same as brain lipoid.

Actions and Uses.—See preceding article, Fibrin Ferments and Thromboplastic Substances.

Dosage.—From 0.1 to 0.2 per cent suspensions of kephalin-Armour in sterile physiological solution of sodium chloride are applied freely to bleeding or oozing surfaces.

Manufactured by Armour and Company, Chicago. No U. S. patent or trademark.

The brain of cattle is desiccated *in vacuo* and the crude phosphatids extracted by means of petroleum ether. This liquid is concentrated and then precipitated with an excess of acetone. The precipitate is extracted with acetone and then with alcohol. The residue is dried and dissolved in ether and the ether solution evaporated to dryness at a low temperature.

Kephalin-Armour is an amorphous, yellowish substance of characteristic odor and taste. It is readily soluble in ether and chloroform, slightly soluble in alcohol and insoluble in acetone. In neutral aqueous solution, it forms an opalescent emulsion. The blood clotting properties of kephalin-Armour are not destroyed by boiling aqueous suspensions of it.

One part kephalin-Armour will coagulate 1,000 parts of oxalated blood plasma in from one to two minutes when tested as follows: One cc. of a 5 per cent solution of kephalin-Armour in ether is added to 25 cc. of physiological solution of sodium chloride and the mixture shaken until a uniform suspension results. Five cc. of this suspension is mixed in a large test tube with an equal volume of blood serum. Ten cc. of oxalated blood plasma (1 Gm. of sodium oxalate in 100 cc. of water added to 900 cc. of fresh blood) are then added and mixed by inverting the test tube twice. The mixture is rapidly transferred to a shallow porcelain dish: it should curdle in from one to two minutes. All solutions used in the preceding test should be made fresh and the temperature of the liquids and the porcelain dish should be maintained at 38 C.

SOLUTION BRAIN EXTRACT.—Liquor Extracti Cerebri.—Solution Thromboplastin-Hess.—An extract of cattle brain in physiological solution of sodium chloride prepared by the method of Hess (*J. A. M. A.* **66**:558 [Feb. 19] 1916, footnote 2).

Actions and Uses.—See preceding article, Fibrin Ferments and Thromboplastic Substances.

Dosage.—The solution may be applied directly to the bleeding tissues or sprayed on them, or a sponge or tampon may be immersed in it and then pressed on the bleeding surface.

Cattle brains are obtained fresh from the slaughter-house, stripped of their membranes, washed in running water and weighed. They are then passed through a meat chopping machine three times, and to the quantity prepared an equal quantity of physiological solution of sodium chloride is added. This suspension is allowed to remain in the refrigerator for forty-eight hours, and is then pressed through cheese-cloth twice. This extract, which contains fine suspension of tissue in addition to tissue juice, is diluted with one half its volume of physiological solution of sodium chloride. Cresol is then added in proper proportion so that the finished preparation contains 0.3 per cent. It maintains its hemostatic potency for some time (several months). (As cresol is not a perfect antiseptic, the sterility of this preparation cannot be guaranteed.)

Thromboplastin Solution-Armour.—An extract of cattle brain in physiological solution of sodium chloride prepared according to the method of Hess. It complies with the description of Solution Brain Extract.

Actions and Uses.—See preceding article, Fibrin Ferments and Thromboplastic Substances.

Dosage.—See Solution Brain Extract. Thromboplastin solution-Armour is marketed in 25 cc. vials which bear an expiration date, after which time the contents should not be used.

Manufactured by Armour & Company, Chicago. No U. S. patent or trademark.

One part of thromboplastin solution-Armour will coagulate 100 parts of oxalated blood plasma in less than one minute when tested as follows: To 0.5 cc. of thromboplastin solution-Armour is added 24.5 cc. of physiological solution of sodium chloride and the mixture shaken until a uniform emulsion results. Of this suspension, 5 cc. is mixed in a graduated cylinder with an equal volume of blood serum. To this is added 10 cc. of oxalated blood plasma (1 Gm. of sodium oxalae in 100 cc. of water, added to 900 cc. of fresh blood) and mixed by inverting the cylinder twice. The mixture is rapidly transferred to a shallow dish; it should coagulate in less than one minute. For this test, all solutions must be made fresh and the temperature of the liquids maintained at 38 C.

Thromboplastin-Lederle.—An extract of cattle brain in physiological solution of sodium chloride prepared according to the method of Hess.

Actions and Uses.—See preceding article, Fibrin Ferments and Thromboplastic Substances.

Dosage.—For local application, see Solution Brain Extract. When local application is not possible, 10 to 20 cc. may be injected subcutaneously or intramuscularly. Thromboplastin-Lederle is marketed in 20 cc. vials which bear an expiration date, after which the contents should not be used.

Manufactured by Lederle Antitoxin Laboratories, New York. No U. S. patent or trademark.

The potency of thromboplastin-Lederle is tested as follows: Oxalated blood plasma is obtained by adding 2.5 cc. of sodium oxalate solution 1 per cent. Transfer 0.5 cc. of oxalated blood plasma to each of a series of tubes, and add 0.2 cc. of thromboplastin-Lederle to each tube. Also transfer 0.5 cc. of oxalated blood plasma to each of a control series of tubes and add 0.2 cc. of physiological solution of sodium chloride. To each tube (and control) add 0.3 cc. of calcium chloride solution (0.5 per cent in physiological solution of sodium chloride): thromboplastin-Lederle must cause clotting of the oxalated blood (such as to permit complete inversion of the tubes) within one minute; the controls must fail to show clotting at the expiration of 20 minutes.

Thromboplastin-Squibb.—An extract of cattle brain in physiological solution of sodium chloride prepared according to the method of Hess. It complies with the description of Solution Brain Extract.

Actions and Uses.—See preceding article, Fibrin Ferments and Thromboplastic Substances.

Dosage.—See Solution Brain Extract. Thromboplastin-Squibb is marketed in 20 cc. vials. It is claimed that no loss of potency could be detected in unopened specimens of thromboplastin-Squibb more than 2 years old.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

Blood plasma is obtained by bleeding 45 cc. of sheep's blood into a tube containing 5 cc. of 1 per cent sodium oxalate in physiological solution of sodium chloride, centrifuging the mixture to obtain the clear plasma and preserving this at a low temperature. A 0.5 per cent calcium chloride solution is prepared by dissolving 0.5 Gm. anhydrous calcium chloride in 100 cc. of physiological solution of sodium chloride. Place 5 drops of blood plasma in a flat bottomed vial, add 3 drops of calcium chloride solution and 2 drops of the thromboplastin-Squibb to be tested and mix the contents by gentle rotation. Not more than sixty seconds should elapse before the vial may be completely inverted without loss of its contents.

Thromboplastin Hypodermic-Squibb.—A sterilized extract of cattle brain in physiological solution of sodium chloride. It complies with the description of thromboplastin-Squibb, but a longer time is required for the clotting of blood plasma.

Actions and Uses.—See preceding article, Fibrin Ferments and Thromboplastic Substances. Thromboplastin hypodermic-Squibb is intended for hypodermic and intramuscular injection to increase the coagulability of the blood.

Dosage.—From 10 cc. to 20 cc. every twenty-four to seventy-two hours. Thromboplastin hypodermic-Squibb is marketed in 20 cc. vials bearing an expiration date, after which the contents should not be used. (The manufacturer reports that no loss of potency could be detected in specimens which had been kept unopened for two years.)

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

Brains from cattle freshly killed are removed under aseptic conditions, using sterile gloves and sterile instruments, and are transferred immediately to sterile containers. They are then taken into a sterile room, where connective tissue, blood vessels, etc., are removed, and the brain substance is thoroughly ground either in a ball mill or sterile meat grinder. The brain substance is then diluted by the addition of physiological solution of sodium chloride containing 0.4 per cent trikresol in the proportion of 8 parts of saline solution to 1 part of brain substance by weight. The reaction of the mixture is then taken, and sufficient sodium hydroxide solution is added to make it neutral to phenolphthalein. It is then poured, under precautions insuring sterility, into sterile bottles which are stoppered with cotton plugs. The resultant mixture is sterilized by streaming steam for forty minutes after a preliminary warming. The result is a slighly opalescent, supernatant fluid overlying the coagulated brain substance. It is then tested for sterility, and when required filled into 20 cc. containers.

FILICIC ACID AND RELATED SUBSTANCES

Aspidium and pharmaceutical preparations thereof have long been used as teniafuges. Aspidium probably contains the following constituents, in approximately the amount indicated: filicic acid, 3.5 per cent; flavaspidic acid, 2.5 per cent; albaspidin, 0.05 per cent; aspidinol, 0.10 per cent; flavaspidin, 0.10 per cent; amorphous acid, 5.0 per cent and filicic nigrine, 60 per cent. These substances are, for the greater part, derivatives of phloroglucinol, and some of them are ketones possessing acid characters.

The various formulas assigned to the filicic acids and the different results reported regarding their physiologic activity have given rise to much confusion, leaving the chemistry in an unsettled condition. One of the first formulas assigned to filicic acid is that of Luck ($C_{28}H_{30}O_9$), which differs considerably from the formula $C_{14}H_{18}O_5$, given this substance by Grabowski, and $C_{14}H_{16}O_5$, as suggested by Dacoma. Later two forms, a crystalline and an amorphous filicic acid, were recognized by Poulson, who suggested the formula $C_{36}H_{40}O_{12}$ for the crystalline filicic acid and $C_{36}H_{42}O_{13}$ for the amorphous acid. The latter he considered the active therapeutic principle of aspidium. Poulson believed the crystalline acid to be the anhydride of the amorphous acid. More recently, Gallas has stated the formula for both the crystalline and the amorphous filicic acid to be $C_{18}H_{22}O_6$. Gallas and later Kraft concluded that one form of the acid was the lactone of the other form. Filicinic acid, which has the formula $C_8H_{16}O_3$, is sometimes confused with filicic acid. Besides a difference in the theories regarding the constitution of the various filicic acids, there has been considerable controversy over the anthelmintic properties of these substances.

Our knowledge of the subject is very imperfect; but the majority of authors still accept filicic acid as one of the active constituents of aspidium.

FORMALDEHYDE PREPARATIONS AND COMPOUNDS WHICH LIBERATE FORMALDEHYDE

The antiseptic actions of formaldehyde cannot be utilized directly on the body because of the irritant and coagulant effects. Attempts have been made to avoid these effects by combining the formaldehyde in such a way as to cause it to be liberated very gradually. The results have been rather disappointing, because it is difficult, if not impossible, to secure just that degree of stability in which the formaldehyde will be liberated in concentrations sufficient to maintain the antiseptic action, but not sufficient to become irritant. Methenamine (hexamethylenetetramine) is a notable exception; but its effects are confined to acid fluids, and, therefore, essentially to the urine. Other compounds are effective mainly through the other constituents with which the formaldehyde is combined, rather than through the formaldehyde itself.

The wide reactivity of formaldehyde gives the possibility of a great variety of compounds; with proteins; carbohydrates; amides; phenols and aromatic derivatives. Methenamine does not contain formaldehyde as such, but liberates it under certain conditions.

Formaldehyde Preparations

PARAFORMALDEHYDE.—For description see the U. S. Pharmacopeia under Paraformaldehydum.

Actions and Uses.—It is converted into formaldehyde by heat, and is therefore used in fumigation. Formaldehyde is also liberated on contact with water, so that paraformaldehyde is antiseptic and escharotic. The rate of liberation, however, is variable, so that its internal employment is not advisable.

Dosage.—Internally, from 0.3 to 1 Gm. (5 to 15 grains); externally (for warts), in 10 per cent suspension in collodion.

SOLUTION OF FORMALDEHYDE.—For description see the U. S. Pharmacopeia under Liquor Formaldehydi.

Actions, Uses and Dosage.—See Useful Drugs.

Formalin.—A brand of solution of formaldehyde-U. S. P.

Schering & Glatz, Inc., Bloomfield, N. J., and New York, N. Y., distributor. U. S. trademark 65,625.

Methenamine and Methenamine Compounds

Hexamethylenetetramine, official as methenamine, owes its action entirely to the liberation of formaldehyde, which occurs only in acid fluids. It is an active urinary antiseptic, provided the urine is secreted in an acid state. It has been shown that no antiseptic effects can occur in the body tissues and fluids which have a neutral or slightly alkaline reaction. Hexamethylenetetramine is not a uric acid solvent, and in gout it has not given satisfactory results.

Its use as a prophylactic against nephritis, especially in scarlatina, has been recommended by several authors. Yet hexamethylenetetramine itself may, at least sometimes, act as a renal irritant. The Council deems it a duty to call attention to this fact, and also to the statement of Jochmann that prophylactic drug treatment, as with hexamethylenetetramine, cannot prevent the nephritis of scarlatina.

Hexamethylenetetramine compounds simply possess the actions of hexamethylenetetramine and of the salts of the acid with which it may be combined.

METHENAMINE.—For description see the U. S. Pharmacopeia and Useful Drugs under Methenamina.

Actions and Uses.—See preceding article, Methenamine and Methenamine Compounds.

Formin.—A brand of methenamine-U. S. P.

Merck & Co., Inc., New York, distributor.
Formin Tablets, 5 grains (0.3 Gm.).
Formin Tablets, 7½ grains (0.5 Gm.).

GELATIN COMPOUND PHENOLIZED-MULFORD.—A mixture composed of gelatin, 625 parts; zinc oxide, 250 parts; glycerin, 1,900 parts; water, 1,900 parts, containing 1.5 per cent of phenol.

Actions and Uses.—Gelatin compound phenolized-Mulford is used in the preparation of bandages to cover chronic ulcers, unhealed secondary burns and the preparation of pressure bandages for varicose veins when surgical treatment is not necessary.

Dosage.—For use, the preparation is heated until it becomes liquid and is applied with a brush; over this a spiral bandage is applied and another layer of the preparation brushed on; this is repeated until a total thickness of three of the bandage and four of the preparation have been applied.

Manufactured by the H. K. Mulford Co., Philadelphia. No U. S. patent or trademark.

HOMOCAMFIN. — Cyclosal. — 3-methyl-5-isopropyl-Δ^2-cyclohexenone dissolved in an aqueous solution of sodium salicylate.

Actions and Uses. — Methylisopropylcyclohexenone, the potent constituent of homocamfin, is claimed to have an action similar to camphor but to surpass it in intensity and rapidity of action on the heart and respiration as shown by animal experiments and clinical observation. This superiority over camphor is due in large part to its solubility in aqueous solution of sodium salicylate which secures prompt absorption.

The most important experimental work on which the claims for homocamfin are based is that of Gottlieb and Schulemann who found that methylisopropylcyclohexenone in the form of homocamfin was two to four times more active than camphor, since in morphinized rabbits an intravenous dose of one milligram stimulated the respiration, while two to four milligrams of camphor dissolved in water were required to produce a similar effect.

While homocamfin is rapidly absorbed when administered intramuscularly, it is absorbed almost instantaneously when administered intravenously; however, the stimulating dose and the convulsant dose are not far apart, and hence caution should be observed when it is used intravenously.

Homocamfin is used as a stimulant in cardiac failure, surgical shock, narcotic poisoning and respiratory failure.

Dosage.—For adults from 1.5 to 2 cc. of homocamfin solution 10 per cent; for children of two to twelve years from 0.5 to 1 cc.

Intravenously for adults 1 cc. of homocamfin solution 1 per cent; but this form of administration is not free from risk and should be reserved for emergencies.

Manufactured by The Bayer Company, Inc., Rensselaer, N. Y. (Winthrop Chemical Co., New York, distributor). U. S. patent 1,477,691 (Dec. 18, 1923; expires 1940). U. S. trademark 203,487.

Ampules Homocamfin 10 per cent (for intramuscular use). Each ampule contains 2.2 cc. of a solution made by dissolving 10 Gm. of *3*-methyl-*5*-isopropyl-Δ *2*-cyclohexenone and 20 Gm. of sodium salicylate in water to make 100 cc.

Ampules Homocamfin 1 per cent (for intravenous use). Each ampule contains 1.2 cc. of a solution made by dissolving 1 Gm. of *3*-methyl-*5*-isopropyl-Δ *2*-cyclohexenone and 25 Gm. of sodium salicylate in water to make 100 cc.

3-methyl-*5*-isopropyl-Δ *2*-cyclohexenone occurs as a light yellowish oil, having a bitter taste. It boils at 127 to 128 C. at 18 mm. pressure. It is soluble in alcohol, ether, benzene and slightly soluble in water. An aqueous solution of 100 cc. containing 10 Gm. *3*-methyl-*5*-isopropyl-Δ *2*-cyclohexenone, and 25 Gm. sodium salicylate is clear at 25 C. With semicarbizid, *3*-methyl-*5*-isopropyl-Δ *2*-cyclohexenone yields a precipitate which on drying melts at 178 to 179 C.

Transfer about 0.2 Gm., accurately weighed, of *3*-methyl-*5*-isopropyl-Δ *2*-cyclohexenone (2 Gm. in case of homocamfin for intramuscular use; or 10 Gm. in case of homocamfin for intravenous use) to a suitable steam distilling apparatus, add 20 cc. of water, followed by about 1 Gm. of magnesium oxide (recently "calcined"), pass steam through the mixture until about 200 cc. of distillate has been collected, transfer the distillate to an Erlenmeyer flask, add 5 cc. of hydrochloric acid and 35 cc. of tenth-normal potassium bromide-potassium bromate solution, stopper the flask with a rubber stopper into which is inserted the small end of a straight drying tube filled with beads moistened with potassium iodide solution, shake the contents of the flask and allow the flask to stand for five minutes; through the drying tube add 20 cc. of potassium iodide solution, shake the solution and titrate quickly the liberated iodine with tenth-normal sodium thiosulphate solution, using starch solution as indicator: each cc. of tenth-normal potassium bromide-potassium bromate solution consumed is equivalent to 0.0076 Gm. of *3*-methyl-*5*-isopropyl-Δ *2*-cyclohexenone; in case of *3*-methyl-*5*-isopropyl-Δ *2*-cyclohexenone, the amount found is not less than 95 per cent nor more than 105 per cent; in case of homocamfin ampules the amount of *3*-methyl-*5*-isopropyl-Δ *2*-cyclohexenone found to be present is not less than 95 per cent nor more than 105 per cent of the claimed amounts.

Transfer the residual mixture after the steam distillation described in the determination for *3*-methyl-*5*-isopropyl-Δ *2*-cyclohexenone to a 500 cc. standard flask, add sufficient hydrochloric acid to make the solution acid and shake the contents until the heavy particles dissolve, add sodium hydroxide solution until alkaline and then add diluted hydrochloric acid until the solution is just acid; transfer an aliquot (25 cc. in the case of homocamfin ampules for intravenous use and 100 cc. in the case of homocamfin ampules for intramuscular use) to an Erlenmeyer flask, add an excess of tenth-normal potassium bromide-potassium bromate solution followed by 5 cc. of hydrochloric acid, stopper the flask quickly with a rubber stopper into which is inserted a drying tube filled with beads and moistened with potassium iodide solution; shake the contents well and then allow the flask to stand twenty minutes; through the drying tube add 20 cc. of potassium iodide solution and allow the flask to stand ten minutes, titrate the liberated iodine with tenth-normal sodium thiosulphate using starch solution as indicator: each cc. of tenth-normal potassium bromide-potassium bromate solution is equivalent to 0.002668 Gm. sodium salicylate; the amount of sodium salicylate is not less than 21.1 per cent nor more than 24.3 per cent in the case of homocamfin ampules for intravenous use; nor less than 17.2 per cent nor more than 19.8 per cent in the case of homocamfin ampules for intramuscular use.

HYDROCHLORIC ACID SUBSTITUTES

Several solid substances have been introduced as medicinal substitutes for hydrochloric acid. It is claimed that these have the action of the free acid in the stomach, but are without the marked acid taste. They also permit the administration of the acid in dry form.

These bodies contain hydrochloric acid in combination with organic substances from which the free acid is readily split off. The physiologic activity of these compounds varies in marked degree with the separability of the hydrochloric acid. The dissociation of the hydrochloric acid, on which the practical value depends, is in some cases nearly complete in aqueous solution, but is much less marked in the case of the large protein-like complexes.

Actions and Uses.—It seems to be possible to secure the antiseptic and digestive action of free hydrochloric acid from some of these products, while from others the liberation of the halogen acid is probably insufficient to accomplish these ends in any marked degree.

BETAINE HYDROCHLORIDE.—Betainae Hydrochloridum. — $C_5H_{11}NO_2.HCl$. — The hydrochloride of betaine, an alkaloid found in the beet, *Beta vulgaris*, and in many other plants.

Actions and Uses.—In the dry state betaine hydrochloride does not split off hydrochloric acid at ordinary temperature. In aqueous solution, betaine hydrochloride is decomposed into betaine and hydrochloric acid (hydrogen chloride). Since betaine has no physiologic action, betaine hydrochloride is a convenient method of administering hydrochloric acid.

Betaine hydrochloride is used for the same purpose as hydrochloric acid.

Dosage.—Five-tenths Gm. (8 grains) which corresponds to about 1.1 cc. (18 minims) of diluted hydrochloric acid-U. S. P., to be taken, dissolved in water.

It consists of colorless crystals, freely soluble in water. It contains 23.8 per cent of absolute hydrochloric acid.

Betaine Hydrochloride-Roche.—A brand of betaine hydrochloride-N. N. R.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J.). No U. S. patent or trademark.

HYPOCHLORITES AND HYPOCHLORITE SUBSTITUTES

The germicidal action of free chlorine and the hypochlorites is well known. In medicine this action has been utilized by the employment of chlorine water, chlorinated lime, solution of chlorinated soda (Labarraque's solution), and solution of chlorinated potassa (Javelle water).

Hypochlorite preparations are fairly permanent in the presence of alkali, and alkaline hypochlorite preparations have the added advantage that the alkali has a destructive and solvent action on most bacteria and other organic matter. In the treatment of infected wounds with hypochlorite solutions at present in vogue, excessive degree of alkalinity is held to be objectionable on the grounds that it causes destruction of normal tissue and irritation of the skin.

Organic preparations containing a chloramide group which are practically neutral and relatively stable have been proposed as substitutes for hypochlorites on the theory that the action of hypochlorites is dependent on the combination of their active chlorine (Cl^+) with nitrogen of proteins.

Hypochlorite Preparations

ANTIFORMIN.—A strongly alkaline solution of sodium hypochlorite. In each 100 cc. it contains approximately: sodium hypochlorite equivalent to 5.68 Gm. available chlorine, sodium hydroxide 7.8 Gm., and sodium carbonate 0.32 Gm.

Actions and Uses.—Antiformin rapidly dissolves the bodies of bacteria with the exception of acid-fast organisms like the tubercle bacillus, on which it has no solvent action and which resists its germicidal action to a great extent. It dissolves other organic matters, such as those contained in sputum and feces. It exerts a strong oxidizing action and is disinfectant, antiseptic and deodorizing. It is said to be more than three times as active in germicidal action as phenol.

Because of its property of dissolving most bacteria and the insoluble constituents of the sputum, antiformin is employed in testing for tubercle bacilli. It is said to be useful for the sterilization of the surgeon's hands, of instruments and of wounds and for general purposes of disinfection. It is also said to be useful in certain skin diseases.

Dosage.—Externally, in from 2 to 10 per cent solution; in a 4 in 1,000 solution as a spray. As a disinfectant 5 per cent solutions are used. For the demonstration of tubercle bacilli, 15 per cent solutions are suitable.

Manufactured by American Antiformin Co., New York. U. S. patent 691,671 (Jan. 1, 1902; expired).

According to the patent specification, chlorinated lime is dissolved in water at 35 C. To this a solution of sodium carbonate is added. After standing, the supernatant liquid is decanted and to this sodium hydroxide is added.

Antiformin is a yellowish, clear liquid having the peculiar odor characteristic of hypochlorites.

The percentage of available chlorin, of alkali hydroxide and carbonate may be determined by the methods described in the Reports of the Chemical Laboratory of the American Medical Association, 1910.

CHLORINE-SODA AMPOULES.—Composed of a sealed glass tube said to contain liquid chlorine (over 99 per cent pure) 4.8 Gm. and a paper container said to contain monohydrated sodium carbonate 21.3 Gm. and yielding when the contents are dissolved in 1,000 cc. of water, a solution similar in composition to surgical solution of chlorinated soda-U. S. P.

To prepare the solution the monohydrated sodium carbonate is placed in a bottle having a capacity of about 2,500 cc. and dissolved in 1,000 cc. of water. The tube containing the liquid chlorine is suspended from a rubber stopper and is inserted into the bottle and the stopper firmly secured. The large bottle (after covering with a cloth) is shaken to break the chlorine tube. The contents of the bottle (without releasing the stopper) are then shaken for two minutes or longer. The solution, freed from particles of glass by decantation or filtration, is then ready for use, or its available chlorine may previously be checked by titration.

Manufactured by Johnson & Johnson, New Brunswick, N. J. No U. S. trademark.

The finished solution contains from 0.45 to 0.50 per cent of sodium hypochlorite. The available chlorine content is determined by titrating 10 cc. in the presence of an excess of potassium iodide and acetic acid, with tenth-normal sodium thiosulphate. For this titration, 12.0 to 13.4 cc. of tenth-normal sodium thiosulphate is required.

To determine whether the solution contains an excess of alkali, a small quantity of powdered phenolphthalein is mixed by rotation with some of the solution contained in a beaker. No red color should be produced.

HYCLORITE.—A solution of chlorinated soda, each 100 Gm. of which is stated to contain sodium hypochlorite 4.05 Gm., sodium chloride 3.20 Gm., calcium hydroxide 0.17 Gm., inert salts 0.92 Gm. It contains not less than 3.85 per cent of available chlorine.

Actions and Uses.—Hyclorite differs from solution of chlorinated soda-U. S. P., chiefly because of the greater content of available chlorine and the lesser degree of alkalinity of the former. It has the actions and uses of solution of chlorinated soda-U. S. P., and when properly diluted it also may be used in the same conditions as those for surgical solution of chlorinated soda-U. S. P. One volume of hyclorite diluted with 7 volumes of water has the same available chlorine content as surgical solution of chlorinated soda, and is isotonic.

Dosage.—Hyclorite is used full strength or diluted with 1 or 2 parts of water for direct application to mucous membrane, muscular tissue, bone infections, etc. For irrigation of wounds, throat and body cavities, dilutions of from 1 in 200 to 1 in 2,000 are used. For use in the irrigation method of treating infected wounds, dilute 1 part of hyclorite with 7 parts of water.

The available chlorine content of hyclorite decreases at the rate of about 12 per cent per year. In order that due allowance for this decrease may be made when diluting for use, each bottle of hyclorite bears the date of bottling.

Manufactured by General Laboratories, Madison, Wis. (Bethlehem Laboratories, Bethlehem, Pa., distributor). No U. S. patent. U. S. trademark 120,110.

Hyclorite is prepared by decomposing chlorinated lime suspended in water with sodium carbonate and adding to the solution obtained a solution produced by electrolysis of a sodium chloride solution.

Hyclorite has the properties of solution of chlorinated soda-U. S. P., but contains no carbonate. When exposed to air, a pellicle forms on its surface owing to the formation of calcium carbonate.

To a definite weight of hyclorite, about 5 grams, is added 50 cc. of distilled water. To the resulting solution, 6 cc. of a 3 per cent hydrogen peroxide solution, previously rendered neutral, is slowly added. After the reaction is completed, which is indicated by the ceasing of the evolution of oxygen, 4 drops of methyl orange indicator solution and an excess (measured) of tenth-normal hydrochloric acid are added, and then the residual acidity determined by titration with tenth-normal sodium hydroxide: the alkalinity found corresponds to not more than 0.17 Gm. of calcium hydroxide per 100 Gm. of hyclorite.

Mix in a flask about 5 cc. of hyclorite, accurately weighed, with 50 cc. of distilled water; add 1 Gm. of potassium iodide and 5 cc. of acetic acid and titrate with tenth-normal sodium thiosulphate, starch test solution being used as indicator: it shows not less than 3.85 per cent of available chlorine.

Each cc. of tenth-normal sodium of thiosulphate used corresponds to 0.003546 Gm. of available chlorine. Due allowance should be made for the decrease in available chlorine content of about 12 per cent per year, date of bottling being stamped on each bottle.

Chloramine Preparations

CHLORAMINE.—For description see the U. S. Pharmacopeia under Chloramina.

Actions and Uses.—The actions of chloramine are essentially similar to those of surgical solution of chlorinated soda-U. S. P. It has the advantages of greater stability, convenience of preparation, and the production of less irritation. On the other hand, it lacks the solvent action of alkaline hypochlorites.

It is practically nontoxic, but should not be used by mouth, since it is decomposed by the gastric juice.

Dosage.—Chloramine is used in 0.1 to 4 per cent aqueous solution. For wounds, the normal strength is from 1 to 2 per cent, applied by the same technic as the surgical solution of chlorinated soda. It has also been employed for irrigation of the urethra, bladder and uterus, and as a mouth wash.

Chlorazene.—A brand of chloramine-U. S. P.

Manufactured by The Abbott Laboratories, North Chicago. No U. S. patent or trademark.

Aromatic Chlorazene Powder: Chlorazene, 5 per cent; sodium bicarbonate, 5 per cent; eucalyptol, 2 per cent; saccharin, 1 per cent; sodium chloride, 87 per cent.

Chlorazene Surgical Cream: Chlorazene 1 Gm. in 100 Gm. of a base composed approximately of sodium stearate 15 per cent and water 85 per cent.

Chlorazene Tablets, 4.6 grains.

Chlorazene Surgical Powder: Chlorazene 1 per cent, zinc stearate 10 per cent and sodium stearate 89 per cent.

Chlorazene Surgical Gauze: Impregnated with and containing approximately 5 per cent of chlorazene.

DICHLORAMINE.—For description see the U. S. Pharmacopeia under Dichloramina.

Actions and Uses.—Dichloramine is an effective germicide through its content of active chlorine (Cl^+). It is only sparingly soluble in water, but soluble in chlorinated eucalyptol or chlorinated paraffin (chlorcosane). The solution produces a gradual, sustained antiseptic action.

It is more irritant than chloramine, but also more solvent. It should not be administered internally.

Dichloramine is claimed to be useful in the prevention and treatment of diseases of the nose and throat; it has been used with success when applied to wounds.

Dosage.—Dichloramine dissolved in chlorinated paraffin (which see) is used in concentrations of from 0.5 to 10 per cent. In nasopharyngeal work from a 1 to a 2 per cent solution is employed; for application to wounds a 5 per cent solution. The solution of dichloramine in chlorinated paraffin is not very stable and should not be kept for more than two or three days. At times the solutions may become irritating to the skin because of the formation of hydrochloric acid. Both dichloramine powder and solution should be protected from sunlight to prevent decomposition.

HALAZONE. — *p*-sulphonedichloramidobenzoic acid. — $C_6H_4(SO_2NCl_2)COOH$-1:4.

Actions and Uses.—Halazone is said to be a powerful disinfectant. It is said to act like chlorine, but to have the advantage of being stable in solid form. In the presence of alkali carbonate, borate and phosphate, Dakin and Dunham report that, in from thirty to sixty minutes, halazone in the proportion of from 1 in 200,000 to 1 in 500,000 sterilized polluted water contaminated with such organisms as *Bacillus coli, Bacillus typhosus, Bacillus paratyphosus* A and B, *Cholera vibrio* and *Bacillus dysenteriae.*

Dosage.—For the sterilization of water, 0.004 to 0.008 Gm. of halazone, in the form of tablets containing sodium carbonate (or sodium borate) and sodium chloride, is added to 1 liter.

Parasulphonedichloramidobenzoic acid was first prepared by H. D. Dakin and E. K. Dunham (Brit. M. J. 1: 682 [May 20] 1917) under the name "Halazone."

Halazone is a white powder having a strong odor of chlorine. It is slightly soluble in water and chloroform; insoluble in petroleum ether;

soluble in glacial acetic acid, benzene, and with the formation of the salt in alkali hydroxide solutions. It crystallizes in stout prisms from glacial acetic acid. The melting point of pure halazone is 213 C.

Halazone liberates iodine from a sodium iodide solution, and bromine from a sodium bromide solution.

If 15 cc. of a saturated aqueous solution of anilin is treated with 0.05 Gm. of halazone, the solution acquires a brownish-red color, which becomes deep blue on supersaturation with ammonia water. If 0.1 Gm. of halazone is treated with a few drops of concentrated sulphuric acid, chlorine is evolved, but no blackening occurs (*readily carbonizable matter*).

About 0.150 Gm. of halazone (or in the case of halazone tablets, 30 tablets), accurately weighed, is dissolved in from 50 to 100 cc. of water and 10 cc. of a 10 per cent sodium hydroxide solution. Fifteen cc. of a 10 per cent potassium iodide solution is added, and the mixture is then acidified with acetic acid and titrated with tenth-normal sodium thiosulphate volumetric solution. (If the reagents used liberate iodine, the number of cubic centimeters of tenth-normal sodium thiosulphate volumetric solution required for their decolorization should be deducted from the total volume used.) The chlorine content of halazone should not be higher than 26.26 per cent or lower than 24 per cent. Each cubic centimeter of tenth-normal thiosulphate volumetric solution is equivalent to 0.00177 Gm. of active chlorine. The thoretical chlorine content of pure halazone is 26.26 per cent.

Halazone-Abbott.—A brand of halazone-N. N. R.

Manufactured by The Abbott Laboratories, North Chicago. No U. S. patent or trademark.

Halazone Tablets-Abbott: Halazone-Abbott, 0.004 Gm., anhydrous sodium carbonate, 0.004 Gm., and sodium chloride enough to make approximately 0.113 Gm.

Halazone-Monsanto.—A brand of halazone-N. N. R.

Manufactured by Monsanto Chemical Works, St. Louis. No U. S. patent or trademark.

INSULIN.—An aqueous solution of an active principle from pancreas which affects sugar metabolism. The strength of insulin is expressed in "units." The unit is equivalent to 0.125 mg. of the international standard preparation of dry insulin hydrochloride prepared by the Medical Council of Great Britain. One mg. of this standard preparation contains eight insulin units, as provisionally defined by the Insulin Committee of the University of Toronto.

Actions and Uses.—Insulin lowers the blood sugar in normal rabbits causing characteristic symptoms when a low level is reached, which symptoms are overcome by the administration of glucose. It prevents the hyperglycemia due to piqure, asphyxia and epinephrine. It increases the sugar consumption of the isolated mammalian heart. It causes glycogen to be deposited in the liver of diabetic animals fed with carbohydrates, and raises the respiratory quotient of such animals. It effects the metabolism of fat in diabetic animals and causes the acetone bodies to disappear from the urine. It has been demonstrated that the administration of insulin to diabetic dogs and to man in severe cases of diabetes mellitus restores temporarily to the body the lost ability to oxidize carbohydrate, and that glycogen is again stored in the liver. If a suitable dose of insulin is administered at suitable intervals to a person suffering from diabetes mellitus, the blood sugar is maintained at a normal level and the urine remains free of sugar; fat is also burned and as a result, ketone bodies do not appear in the urine and diabetic acidosis and coma are prevented.

The administration of insulin is indicated in cases of diabetes mellitus which cannot be controlled at a satisfactory level by dietetic treatment. In such cases, with proper regulation of the diet, insulin should be administered in such amounts as to prevent glycosuria and a too great hyperglycemia. In some cases the dosage of insulin may be gradually decreased as the body power of utilizing carbohydrate returns toward normal.

Overdosage of insulin is followed by the development of serious symptoms which demand immediate treatment. The patient complains of weakness and fatigue and a feeling of nervousness or tremulousness. This is followed by profuse sweating, which is the most characteristic sign of overdosage. There is sometimes pallor or flushing. In the more severe forms there is acute distress with mental disturbances and even unconsciousness. These symptoms are relieved by the administration of some form of soluble carbohydrate, such as orange juice, by mouth or stomach tube, or, if the patient is comatose, by the intravenous injection of from 5 to 20 grams of pure dextrose in a 5 to 50 per cent sterile solution. Although symptoms of hypoglycemia usually develop gradually, the onset in occasional cases may be sudden. In view of this, ambulant patients should be instructed to carry, for immediate use, soluble carbohydrate in the form of powdered dextrose or an orange. Physicians treating patients with insulin should be impressed with the necessity of having adequate supplies of sterile solution of glucose at hand. In case of emergency when sterile solution of glucose is not available, a subcutaneous injection of 0.3 cc. to 0.6 cc. of 1 in 1,000 solution of epinephrine may be employed, but this must always be followed by carbohydrates by mouth. The injection of epinephrine must be employed carefully as its action depends on the presence of glycogen, of which there is usually very little in the diabetic organism, and it should never be employed when the hypoglycemia follows excessive exercise.

Dosage.—Insulin is administered by injection into the loose subcutaneous tissue of the body, usually 0-30 minutes before meals. There is no average dose of insulin for diabetics; each case must be studied individually. Except when complications occur insulin is not indicated when a patient has adequate glucose tolerance to provide him with a diet sufficient for light work. The dose depends upon the amount of glucose in such a diet as he is unable to metabolize; i. e., the glucose excretion on a known diet. A convenient formula is: $\frac{\text{Average gms. glucose excreted}}{1.5}$ = sufficient units of insulin to render most patients aglycosuric. Usually the daily dose is administered in two equal portions, one before breakfast and the other before supper. The carbohydrate of the diet should be distributed evenly between the three meals. With large daily dosage (40 units or more) insulin may be injected before each meal. When the patient becomes aglycosuric the diet can usually be increased. Sufficient insulin should be used to keep the fasting blood sugar normal, but hypoglycemia should be avoided. If patients are not under close observation, half the estimated dose may be used and the dose gradually increased until therapeutic results are obtained.

In cases of coma or severe acidosis an initial dose of 30-60 units may be given (in coma intravenously) followed at 3-4 hour intervals by doses of 20 units or more subcutaneously. Administer one gram of glucose for each unit of insulin used. The patient should never become hypoglycemic. Examine the urine hourly for glucose. If urine becomes sugar free more glucose must be given. More than 150 units of insulin in twelve hours is rarely needed.

In a small number of cases of diabetes mellitus, insulin can be discontinued, particularly with patients who receive it because of an exacerbation caused by complications, and where diabetes is of recent onset (though perhaps the latter should receive it intermittently as a prophylactic against increasing severity).

Dosage of insulin should always be expressed in units rather than in cubic centimeters or minims. The *volume* of any one prescribed dose of insulin will vary with the strength of the solution which is employed.

The animals used as test subjects and controls are rabbits, unselected as to sex, breed or color, free of any visible sign of infection, and weighing from 1.8 Kg. to 2.2 Kg. Each animal is used once each week as long as it remains suitable in all respects for use, particularly as regards weight. A record of each animal's reaction towards insulin is kept, in order that those showing marked irregularities on more than one occasion may be discarded. Test animals are kept on a diet of hay and oats, carrots being allowed once each week with the first post-assay meal. All new rabbits are placed on this diet for two weeks prior to being first used. Twenty-four hours before rabbits are to be used, all food is removed from their cages, water being allowed to remain.

In assaying a sample of insulin the approximate potency of which is unknown, a rough indication of its potency is first obtained by injecting a number of animals (say, eighteen) with a widely varying number of doses per 2 Kg. bodyweight (say, six) and noting the lowest dose which produces convulsions in the majority of animals injected with that dose. This so-called "convulsant dose" is then considered as about 3 units. For the determinative assay, eighteen rabbits are used each day. Each of these rabbits is weighed and a normal blood sample is taken from it. Then three doses of the insulin sample under assay, diluted with acid water (*p*H 2.5) so that there are presumably 2.5 units in each cc. of solution, are injected subcutaneously into three equal groups of three animals—2.5 units, 2.0 units and 1.5 units per 2 Kg. bodyweight being given to each animal of the first, second and third groups, respectively. Similarly, three doses of the International Insulin Standard, diluted with acid water (*p*H 2.5) so that there are 2.5 units in each cc. of solution, are injected into three equal groups of three animals—2.5 units, 2.0 units and 1.5 units per 2 Kg. bodyweight being given to each animal of the first, second and third of these groups, respectively. At intervals of 1½ 3 and 5 hours after injection, a sample of blood is withdrawn from each animal. The samples of each bleeding are pooled in equal quantities and the sugar content of these and of the normal blood samples is determined by a suitable method, such as that of Shaffer and Hartmann (*Jour. Biol. Chem.*, 1920, XLV, 365). Calculations are then made, using the following equation:

$$\text{Units per cc.} = \frac{a}{b} \times \frac{w}{c} \times 1.5$$

where

a = percentage of blood-sugar before injection minus the averages of the percentages of blood-sugar found in the samples taken 1½, 3 and 5 hours after injection.
b = percentage of blood-sugar before injection minus 0.045 per cent.
w = weight of rabbit in Kg.
c = number of cc. of the original (undiluted) insulin injected.

For the sample under assay on the one hand, and for that used as a standard (a solution standardized upon the International Insulin Standard) on the other, the averages of the results arising out of the above equation on the first day are compared, and the dilution of the unknown sample is then adjusted from day to day until the two averages become practically identical and remain so for at least three days of confirmatory testing. The potency of the sample under assay may then be arrived at by simple arithmetical calculation.

The doses used in the Insulin Committee Laboratory ordinarily occasion convulsions in about 20 to 25 per cent of the animals injected. These convulsions may be readily antidoted by an injection of dextrose either intravenously or subcutaneously; but this course should be followed only where an animal is lost to a test through failure to bleed, or where death due to respiratory failure is imminent.

U. S. patent 1,469,994 (Oct. 9, 1923; expires 1940), 1,470,024 (Oct. 9, 1923; expires 1940), 1,520,673 (Dec. 23, 1924; expires 1941). Canadian patents 234,336 and 234,337. U. S. trademark 179,174. Canadian trademark 31,646.

Insulin-Mulford.—A brand of insulin.

Manufactured by H. K. Mulford Co. under license from the Governors of the University of Toronto.

Insulin-Mulford 10 Units, 5 cc.: Each cubic centimeter contains 10 units.

Insulin-Mulford 20 Units, 5 cc.: Each cubic centimeter contains 20 units.

Insulin-Mulford 40 Units, 5 cc.: Each cubic centimeter contains 40 units.

Insulin-Mulford, 10 Units, 10 cc.: Each cubic centimeter contains 10 units.

Insulin-Mulford, 20 Units, 10 cc.: Each cubic centimeter contains 20 units.

Insulin-Mulford, 40 Units, 10 cc.: Each cubic centimeter contains 40 units.

Insulin-Mulford, 80 Units, 10 cc.: Each cubic centimeter contains 80 units.

Beef pancreas is rendered as free from fat and connective tissue as possible, and extracted with acidulated 60 per cent alcohol. The mixture is centrifugalized and the gland residue reextracted with 60 per cent alcohol. The alcoholic liquid is then concentrated to about one-twelfth its original volume. The active substance is then precipitated with ammonium sulphate, and reprecipitated from an alcoholic solution. It is further purified by a method of iso-electric precipitation and is finally dissolved in acid water (*p*H 2.5) and preserved by the addition of 0.1 per cent cresol. It is then filtered through a Berkefeld filter, and submitted to sterility tests; its potency is determined by the method described under the preceding article, "Insulin."

Insulin-Squibb.—A brand of insulin.

Manufactured by E. R. Squibb and Sons, New York, under license from the Governors of the University of Toronto.

Insulin-Squibb, 10 Units, 5 cc.: Each cubic centimeter contains 10 units.

Insulin-Squibb, 20 Units, 5 cc.: Each cubic centimeter contains 20 units.

Insulin-Squibb 40 Units, 5 cc.: Each cubic centimeter contains 40 units.

Insulin-Squibb, 10 Units, 10 cc.: Each cubic centimeter contains 10 units.

Insulin-Squibb, 20 Units, 10 cc.: Each cubic centimeter contains 20 units.

Insulin-Squibb, 40 Units, 10 cc.: Each cubic centimeter contains 40 units.

Insulin-Squibb, 80 units, 10 cc.: Each cubic centimeter contains 80 units.

Insulin-Squibb, 100 units, 10 cc.: Each cubic centimeter contains 100 units.

Insulin-Squibb is made by extracting finely ground beef pancreas with acidulated aqueous alcohol and subsequently removing the tissue by centrifuging. The alcoholic solution is concentrated and the insulin is precipitated by ammonium sulphate after the removal of fats. This sulphate precipitate is dissolved in dilute ammonia and impurities removed by alcohol precipitation. From the above filtrate the insulin is precipitated with ether and redissolved in ammonia. It is then reprecipitated at its iso-electric point *p*H 4.8-5.2. This nearly pure insulin precipitate is centrifuged and dissolved in acid water which is then passed through a Berkefeld filter and assayed.

Insulin-Stearns.—A brand of insulin.

Manufactured by Frederick Stearns and Company, Detroit, under license from the Governors of the University of Toronto. No U. S. trademark.

Insulin-Stearns, 10 Unit, 5 cc.: Each cubic centimeter contains 10 units.

Insulin-Stearns, 20 Unit, 5 cc.: Each cubic centimeter contains 20 units.

Insulin-Stearns, 40 Unit, 5 cc.: Each cubic centimeter contains 40 units.

Insulin-Stearns, 10 Unit, 10 cc.: Each cubic centimeter contains 10 units.

Insulin-Stearns, 20 Unit, 10 cc.: Each cubic centimeter contains 20 units.

Insulin-Stearns, 40 Unit, 10 cc.: Each cubic centimeter contains 40 units.

Insulin-Stearns, 80 Unit, 10 cc.: Each cubic centimeter contains 80 units.

The method of preparation of insulin-Stearns is essentially that described in the *Journal of Biological Chemistry*, October, 1923, p. 717, *et seq.* The potency of insulin-Stearns is determined by the method described under the preceding article, "Insulin." Dilution of concentrated solutions to proper strength is made with sterile distilled water with a *p*H of 2.5 and 0.1 per cent cresol is added. Final filtration is carried on through sterile Berkefeld filters, and the material is filled into sterile vials. Corroborative tests for unit-strength and sterility are determined before any lot is released for use.

Insulin-Toronto.—A brand of insulin.

Manufactured by the Connaught Laboratories, University of Toronto, Toronto, Canada.

Insulin-Toronto, 10 Units, 5 cc.: Each cubic centimeter contains 10 units.

Insulin-Toronto, 20 Units, 5 cc.: Each cubic centimeter contains 20 units.

Insulin-Toronto, 10 Units, 10 cc.: Each cubic centimeter contains 10 units.

Insulin-Toronto, 20 Units, 10 cc.: Each cubic centimeter contains 20 units.

The method of preparation of insulin-Toronto is essentially as described in the *Journal of Biological Chemistry*, October, 1923, p. 717 *et seq.*

After a solution of insulin has been prepared, its potency is determined in the manner described under Insulin. The solution is then diluted, if necessary, with sterile distilled water of a correct *p*H concentration (usually 2.5) to the desired strength and 0.1 per cent cresol is added. The solution is then passed through a sterile Mandler filter and the potency of the filtered solution is determined again by the accepted method. The liquid is then filled into vials. A number of vials of each lot are set aside and the sterility of these is determined before the remainder is released.

Iletin (Insulin-Lilly).—A brand of insulin.

Manufactured by Eli Lilly & Co., Indianapolis, Ind., under license from the Governors of the University of Toronto. U. S. trademark 171,971.

Iletin (Insulin-Lilly) U-10, 5 cc.: Each cubic centimeter contains 10 units.

Iletin (Insulin-Lilly) U-20, 5 cc.: Each cubic centimeter contains 20 units.

Iletin (Insulin-Lilly) U-40, 5 cc.: Each cubic centimeter contains 40 units.

Iletin (Insulin-Lilly) U-10, 10 cc.: Each cubic centimeter contains 10 units.

Iletin (Insulin-Lilly) U-20, 10 cc.: Each cubic centimeter contains 20 units.

Iletin (Insulin-Lilly) U-40, 10 cc.: Each cubic centimeter contains 40 units.

Iletin (Insulin-Lilly) U-80, 10 cc.: Each cubic centimeter contains 80 units.

Iletin (Insulin-Lilly) U-100, 10 cc.: Each cubic centimeter contains 100 units.

Fresh pancreatic glands of animals, from which fat and connective tissue have been removed, are ground, and extracted with 1½ volumes 95 per cent alcohol, containing 0.11 per cent absolute sulphuric acid. The mixture is agitated during two hours and then filtered. The residue is again extracted using an equal volume of 70 per cent alcohol containing 0.11 per cent absolute sulphuric acid. This is filtered, and the filtrate added to the first filtrate. The combined filtrates are chilled to 0 C. and filtered. The filtrate is concentrated to about one-twenty-fifth its original volume, filtered, and the filtrate added to 5.3 times its volume of 95 per cent alcohol. This mixture is allowed to stand for several hours, and then filtered, and the filtrate made up to contain 93 per cent alcohol. After standing several days, the precipitate formed is collected and dissolved in distilled water. The insulin preparation is further purified by precipitation at the isoelectric point, the hydrogen ion concentration being adjusted to approximately *p*H 4.7, after which the solution is allowed to stand in the icebox. The precipitate formed is dissolved in acidified water (*p*H 2.5), filtered, reprecipitated and redissolved if necessary for further purification. The solution is then diluted to approximately the desired potency, filtered through a Berkefeld filter, and submitted to standardization and sterility tests.

IODINE COMPOUNDS

Iodine compounds are used partly for their local irritant and antiseptic effects, which are due probably to the action of free iodine contained in the preparations or liberated from them, and partly for their systemic actions. These may be discussed separately under the headings of "Iodine Preparations Containing Free Iodine," "Iodine Dusting Powders," and "Iodine Compounds for Internal Use."

Iodine Preparations Containing Free Iodine

IODINE.—For description see the U. S. Pharmacopoeia and Useful Drugs under Iodum.

Iodosticks, Iodoapplicators and Special Iodoapplicators (Iodine 60 per cent and Potassium Iodide 40 per cent): Wooden sticks, 3.8, 14.0, 16.5 and 30.5 cm. (1½, 5½, 6½ and 12 inches) long, respectively, tipped with a mixture of iodine, 60 per cent and potassium iodide, 40 per cent. Each stick is to be used but once.

Prepared by Tappan Zee Surgical Co., Nyack, N. Y.

IOCAMFEN.—A liquid obtained by the interaction of iodine 10 parts, phenol 20 parts and camphor 70 parts, containing about 7.25 per cent free iodine.

Actions and Uses.—Iocamfen is said to have the antiseptic and germicidal properties of iodine and also the analgesic, stimulating and antiphlogistic properties of camphor and phenol.

Iocamfen is used especially in the treatment and dressing of surgical and traumatic wounds, joint injuries, fractures, infected processes, contusions, etc.

Dosage.—Iocamfen is applied in small quantities directly to wounds, the skin, cavities, etc., or on tampons or drainage material. It should not be applied to wet surfaces.

Manufactured by Schering & Glatz, Inc., Bloomfield, N. J., and New York. No U. S. patent. U. S. trademark 112,934.

Iocamfen is a dark, reddish-brown, viscid liquid, having a camphoraceous odor. Iocamfen is insoluble in water, but soluble in all proportions in alcohol, ether, benzine and liquid petrolatum.

Iocamfen, like free iodine, interacts with fats and waxes, its free iodine entering into combination.

The free iodine content of iocamfen may be determined thus: About 2 Gm. iocamfen is weighed into a glass-stoppered flask, dissolved in about 25 cc. of chloroform, about 10 cc. of potassium iodide solution (1 in 10) added, and the free iodine determined by titration, under agitation, with tenth-normal sodium thiosulphate solution, using starch as an indicator.

Iodine Dusting-Powders

Dusting-powders containing iodine in various combinations are widely used in the treatment of wounds, granulating surfaces, abscess cavities, etc., whether due to syphilis or tuberculosis or to other infections. The virtue of such preparations was formerly attributed to a germicidal action, but investigators have found such action very slight. The clinical results are now ascribed to a slight antiseptic action of the iodine, to a stimulation of phagocytosis, and to a diminished secretion of the wound which renders it a less favorable culture medium for germs.

Iodoform has been the standard drug of this class. Other insoluble organic iodine compounds have been introduced to replace iodoform, but with limited success. While they avoid the disagreeable odor and the occasional toxic systemic effects, they also lack much of the efficiency.

THYMOL IODIDE.—For description see the U. S. Pharmacopeia and Useful Drugs under Thymolis Iodidum.

Aristol.—A brand of Thymol Iodide-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. trademark 17,393.

VIOFORM-CIBA. — Iodochlorhydroxyquinolin. — $C_9H_4N.OH.I.Cl$.—A substitution compound of anachlor-ortho-hydroxyquinoline resulting from the introduction of one atom of iodine.

Actions and Uses.—Vioform-Ciba is used as an odorless substitute for iodoform.

Dosage.—Vioform-Ciba is used as a dusting powder for application to wounds, ulcers, burns, exudative skin eruptions, etc.

Manufactured by the Society of Chemical Industry in Basle, Switzerland (Ciba Co., Inc., New York). U. S. patent 641,491 (Jan. 16, 1900; expired). U. S. trademark 92,732.

Vioform-Ciba is a grayish-yellow, odorless powder, almost insoluble in water, sparingly soluble in alcohol, soluble in hot glacial acetic acid.

Boil vioform-Ciba with dilute hydrochloric acid: it dissolves slowly, evolving an odor of iodine. Treat a specimen of vioform-Ciba with concentrated sulphuric acid: copious vapors of iodine are evolved. Repeatedly crystallize vioform-Ciba from hot glacial acetic acid: crystals are obtained which melt at 178 to 180 C.

Mix about 0.5 Gm. of vioform-Ciba, accurately weighed, in a nickel crucible with a mixture of powdered sodium hydroxide 4 parts and potassium nitrate 1 part, and heat until fusion has been completed. Cool and dissolve the fused mass in 150 cc. of water, warming to hasten solution; filter into a 400 cc. beaker and wash well. Add 25 cc. of tenth normal silver nitrate (the amount of silver is k in the formula below); then add slowly, with stirring, nitric acid until acid in reaction to litmus paper. Filter the solution through a weighed Gooch crucible, wash and titrate the excess silver nitrate in the filtrate with tenth normal potassium sulphocyanate (the amount of silver in the filtrate is a). The precipitate in the Gooch crucible (consisting mainly of silver iodide with some silver chloride) is further washed with 3 portions of alcohol, then ether, dried at 100 C. and weighed (w). The amount of iodine can be calculated according to the formula

$$x = \frac{0.7527\ w + a - k}{293}$$

where w equals combined weight of silver iodide and silver chloride; x equals weight of silver iodide and $(w\text{-}x)$ equals weight of silver chloride: by this method Vioform-Ciba contains not less than 37.5 per cent nor more than 41.5 per cent of iodine, and not less than 11.5 per cent nor more than 12.2 per cent of chlorine.

Iodine Compounds for Systemic Use

These are typified by the ordinary iodides. The mechanism of their action is not understood. The most definite results are seen in the rapid absorption of certain inflammatory exudates and especially of the tertiary lesions of syphilis (gummas). Lesions of the bone, skin, brain, or other internal organs, disappear under adequate doses of the drug. Likewise, in actinomycosis and sporotrichosis, the action of iodine as iodide is almost specific. The iodides are not germicidal.

The effect of iodides in arteriosclerosis and aneurysm is probably limited to the absorption of syphilitic deposits in the vessel wall. The iodides do not directly lower blood pressure. They increase the amount of thyreoprotein and may thus have indirect effects on metabolism.

COMPLEX IODINE COMPOUNDS

Iodine compounds with proteins and fats have been introduced with claims that they are less irritating to the digestive tract and that they are less inclined to set up the disagreeable symptoms of iodism, for instance, coryza and skin eruptions. Experience confirms in a measure the former claim, but the latter is misleading. Iodism is probably a necessary manifestation of the full physiologic activity of the drug, which is required for the treatment of syphilis and other diseases. If, therefore, a preparation fails to elicit these characteristic symptoms, we conclude that the amount of the drug absorbed is insufficient. Clinical observations show that the organic iodides, in the dosage ordinarily employed, are weaker than the metallic forms.

The approximate percentage of iodine in the official iodides and in the organic compounds of iodine listed in New and Nonofficial Remedies is given in the following table:

	Per Cent
Iodalbin	21.5
Iodipin 10 per cent	9.8–11.2
Iodipin 40 per cent	39.0-41.0
Iodocasein	18.0
Iodostarine-Roche	47.5
Iothion	77.0–80.0
Lipoiodine-Ciba	41.0
Lipiodol-Lafay	39-41
Lipiodol Radiologique Ascendant	9.8-11-2
Lipiodol Radiologique Descendant	34-36
Oridine	23.0–25.0
Potassium Iodide	76.4

	Per Cent
Riodine	17.0
Calcium Iodobehenate, Sajodin	23.5
Ferro-Sajodin	24.0
Sodium Iodide	84.6
Stearodine	26-28
Strontium Iodide	56.5
Thymol Iodide, Aristol	45.0

The following preparations are included in New and Nonofficial Remedies:

Aristol: A brand of thymol iodide-U. S. P.

Iodalbin: A compound of iodine and blood albumin.

Iodipin: An iodine addition product of sesame oil.

Iodo-Casein: A compound of iodine with milk casein.

Iodostarine-Roche: An iodine addition product of tariric acid.

Iothion: Diiodohydroxypropane.—$CH_2I.CH(OH).CH_2I$.

Lipoiodine-Ciba: Ethyl diiodobrassidinate. — $C_{21}H_{39}I_2COO(C_2H_5)$.

Lipiodol-Lafay: An iodine addition product of poppy seed oil.

Oridine: The calcium salt of the iodized fatty acids of cottonseed oil.

Riodine: An iodine addition product of castor oil.

Sajodin: A brand of calcium iodobehenate.—U. S. P.

Ferro-Sajodin: Basic ferric iodobehenate, approximately, $Fe(OH)(C_{21}H_{42}ICOO)_2$.

Stearodine: Calcium Iodostearate. — $Ca[CH_3(CH_2)_7CHI(CH_2)_8CO_2]_2$.

IODINE—PROTEIN COMPOUNDS

IODALBIN.—A compound of iodine and blood albumin, containing approximately 21.5 per cent of iodine.

Actions and Uses.—When administered to animals, iodalbin appears to suffer little change in the acid contents of the stomach; but on passing into the intestines, it is dissolved by contact with the alkaline secretion and on absorption exerts a physiologic action similar to that of the soluble iodides. It is indicated in the same cases as the soluble iodides.

Dosage.—From 0.3 to 0.6 Gm. (5 to 10 grains) repeated according to indications, or until the desired effects are obtained.

Manufactured by Parke, Davis & Company, Detroit. No U. S. patent or trademark.

Iodalbin Capsules, 5 grains.

Iodalbin and Mercurol Tablets: Iodalbin, 5 grains (0.32 Gm.), and mercurol, 1 grain (0.06 Gm.).

Iodalbin is prepared by treating blood albumin with a solution of iodine whereby an insoluble precipitate is produced. This precipitate is separated, purified by the removal of free iodine, dried, powdered and assayed.

Iodalbin is a reddish-colored powder, practically tasteless and possessing a peculiar, rather pleasant odor, suggestive of cane syrup or molasses. It is almost insoluble in water, acids, alcohol and other ordinary solvents, but is readily soluble in strong alkaline solutions; more slowly soluble in dilute alkaline solutions. When heated, it evolves iodine vapors copiously and is subsequently consumed to an ash, leaving a small amount of residue.

The presence and amount of iodine can be determined by the usual processes for detecting and estimating this element in organic substances.

IODO-CASEIN. — Casein-Iodine. — A compound of iodine with milk casein, containing about 18 per cent of iodine in organic combination.

Actions and Uses.—This drug is said to undergo practically no change in the stomach, but to be quickly digested in the intestines and absorbed in the form of soluble iodides. It is claimed that iodo-casein may be used to advantage as a substitute for the inorganic iodides, since it is absorbed more gradually and lacks the saline taste.

Dosage.—From 0.3 to 1.3 Gm. (5 to 20 grains), as indicated. For goiter prophylaxis, the equivalent of 0.01 Gm. iodine, or about 0.05 Gm.

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

Iodo-Casein Tablets, 5 grains (0.3 Gm.).

Tablets Iodo-Casein with Chocolate: Each tablet contains iodo-casein equivalent to 0.01 Gm. iodine.

Iodo-casein is prepared by treating a solution of casein in sodium carbonate with a solution of iodine and precipitating with acetic acid.

Iodo-casein is a yellowish-brown powder, almost odorless and tasteless, insoluble in water, or acid solutions. It is partially dissolved and decomposed by alkalis.

IODIZED FATS AND FATTY ACIDS

Iodized fats and iodized fatty acids produce in general the same systemic effects as ordinary (inorganic) iodides; but their iodine is more slowly absorbed and excreted, and therefore more persistently retained in the tissues; especially in tissues rich in lipoids, such as the nervous structures.

The iodized fats and fatty acids generally pass the stomach unchanged, and are saponified and absorbed in the small intestine, like ordinary fats. They are then deposited for the most part in lipoid tissues, where they are gradually oxidized, yielding inorganic iodide, which is given off to the blood and excreted. The iodine content of the blood is thus maintained more uniform than when inorganic iodides are administered.

It is conceivable that iodized fats and fatty acids have therapeutic advantages over ordinary iodides, when a gradual, long-sustained iodide action is desired; but the clinical evidence is not decisive. The doses used in these conditions as a rule are not irritating to the stomach and are not likely to produce iodism.

IODIPIN 10 PER CENT.—Iodized Sesame Oil 10 per cent-Merck. An iodine addition product of sesame oil containing from 9.8 to 11.2 per cent of iodine in organic combination.

Actions and Uses.—Iodipin 10 per cent is used as a substitute for the inorganic iodides over which it is claimed to have an advantage in that it is longer retained and therefore better utilized. See preceding article, Iodized Fats and Fatty Acids.

Dosage.—From 4 to 8 Gm. (60 to 120 grains), three or four times a day. Iodipin 10 per cent should be exposed to the light to prevent its darkening.

Supplied in the form of tablets only.

Marketed by Merck & Co., Inc., Rahway, N. J., by license of Chemical Foundation, Inc., under U. S. patent 774,224 (issued Nov. 8, 1904; expired). U. S. trademark 32,003.

Tablets Iodipin 10 per cent-Merck: Iodipin 10 per cent Merck—8 grains.

Iodipin 10 per cent, is a yellow, oily liquid, having a purely oleaginous taste. It is insoluble in water.

If to 1 cc. of iodipin in 10 cc. of chloroform a few drops of phenolphthalein solution are added, the addition of 0.3 cc. (1 drop) of half-normal sodium hydroxide should produce a red color (*limit of acidity*).

Boil 1 Gm. of Iodipin, accurately weighed, for a few minutes in a small flask with 15 cc. of alcohol and 3 Gm. of potassium hydroxide, transfer the liquid to a porcelain dish, evaporate on the water bath and incinerate the residue over a gentle flame. Dissolve the ash in water, make up to 100 cc. and filter. To 25 cc. of the filtrate add 3 cc. of 25 per cent hydrochloric acid and 50 cc. of freshly prepared chlorine water and boil until the excess of chlorine is expelled. Cool, add 2 Gm. of potassium iodide and titrate the liberated iodine with tenth-normal sodium thiosulphate: the amount of the iodine found is not less than 9.8 per cent, nor more than 11.2 per cent.

IODIPIN 40 PER CENT.—Iodized Sesame Oil 40 Per Cent-Merck.—An iodine addition product of sesame oil containing from 39 to 41 per cent of iodine in organic combination.

Actions and Uses.—Iodipin 40 per cent, on account of its high molecular weight, is used as a contrast medium in myelography for detecting urethral strictures and in the spinal column for the location of tumors.

Dosage.—From 1 to 5 cc. (15 to 75 minims).

Marketed by Merck & Co., New York, by license of the Chemical Foundation, Inc., under U. S. patent 774,224 (issued November 8, 1904; expired) and U. S. trademark 32,003.

Ampules Iodipin 40 Per Cent. 2 cc.

Iodipin 40 per cent is an oily liquid, insoluble in water, having an oleaginous taste. Its color is brown to black, depending on the thickness of the layer that is examined. Specific gravity at 15 C., from 1.370 to 1.372.

Boil 0.5 cc. of iodipin 40 per cent and 10 cc. of alcoholic solution of potassium hydroxide (1 in 10), in a porcelain dish for about five minutes, evaporate the liquid on a water bath and ignite the residue. Dissolve the residue in 10 cc. of water, filter the solution, add 5 cc. of hydrochloric acid to the filtrate, then add chloroform and a few drops of chlorine water and agitate: the chloroform solution is violet. Dissolve 1 cc. of iodipin 40 per cent in 10 cc. of chloroform, add a few drops of phenolphthalein solution and 0.3 cc. (1 drop) of tenth-normal sodium hydroxide: the liquid becomes red (*limit of acidity*). Mix 10 cc. of iodipin 40 per cent with 50 cc. of petroleum benzin: a transparent liquid results.

Transfer into an Erlenmeyer flask about 0.5 Gm. of iodipin 40 per cent, weighed accurately; add 15 cc. of alcoholic solution of potassium hydroxide (potassium hydroxide, 3 Gm., in alcohol, strength 85.8 to 87.3 per cent by weight, 15 cc.) and boil the mixture for five minutes under a reflux condenser. Evaporate the liquid in a porcelain dish on a water bath and ignite the residue carefully. Dissolve the residue in water, transfer it to a 100 cc. measuring flask, dilute to exactly 100 cc. and filter (part of the filtrate is used for "a" and part for "b"). (*a*) To 20 cc. of the filtrate add 3 cc. of hydrochloric acid (sp. gr. 1.126 to 1.127) and 50 cc. of freshly prepared chlorine water, boil the mixture until the excess of free chlorine is expelled, cool the solution, add an excess of potassium iodide and titrate the liberated iodine with tenth-normal sodium thiosulphate solution: the weight of iodine found corresponds to not less than 39 per cent nor more than 41 per cent. (*b*) To 50 cc. of the filtrate add 10 cc. of nitric acid (sp. gr. 1.150 to 1.152) and 10 cc. of tenth-normal silver nitrate solution, agitate thoroughly and determine the excess of silver nitrate by titration with tenth-normal ammonium thiocyanate solution, using ferric ammonium sulphate as indicator: the amount of iodine found by this method agrees with that found by method (*a*) (*limit of chlorine or bromine*).

IODOSTARINE-ROCHE.—Diiodotariric acid.—$C_{18}H_{32}I_2O_2$.—An iodine addition product of tariric acid, $C_{18}H_{32}O_2$, derived from the fruit of a species of *Picramnia.* Iodostarine-Roche contains 47.5 per cent of iodine.

Actions and Uses.—Iodostarine-Roche is used as a substitute for the inorganic iodides over which it is claimed to have an advantage in that it is longer retained and therefore better utilized. See preceding article, Iodized Fats and Fatty Acids.

Dosage.—The same as that of potassium iodide. Marketed in the form of tablets only.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J.). U. S. patent 982,656 (Jan. 24, 1911; expired 1928) and U. S. trademark 87,996.

Tablets Iodostarine-Roche, 0.25 Gm.

Chocolate Tablets Iodostarine-Roche: Each contains iodostarine-Roche equivalent to iodine 0.01 Gm. This dosage form is used only for prophylaxis against goiter and for the treatment of simple goiter.

Iodostarine-Roche is a white, crystalline solid, odorless and tasteless. It is insoluble in water; slightly soluble in cold alcohol; soluble in warm alcohol, ether, chloroform, benzene and carbon disulphide. It is permanent in the air. It melts at 48 to 49 C.: at a higher temperature it decomposes with evolution of iodine.

To about 1 Gm. of iodostarine-Roche, accurately weighed, add 50 cc. of half-normal potassium hydroxide in methyl alcohol. Heat for two hours under a reflux condenser. Remove the condenser, boil off the alcohol, taking care to avoid loss by bumping, and transfer the residue to a separator, using at first warm water, but finally a little diluted nitric acid to insure complete transfer of the iodide to the separator. Cool and add 50 cc. of ether and sufficient diluted nitric acid to decompose the soap. If the solution becomes yellow from liberation of iodine add a little sodium sulphite to reduce the iodine. Shake thoroughly and draw off the acid layer through a wetted filter into a 500 cc. flask. Wash the ether in the separator with three separate portions of water of 25 cc. each, adding these through the filter to the acid solution in the flask, warm to expel dissolved ether, cool, and add 5 cc. of concentrated nitric acid and, at once, 25 cc. of tenth-normal silver nitrate. Titrate the excess of silver with tenth-normal potassium sulphocyanate, using ferric ammonium sulphate as indicator: the volume of tenth-normal silver nitrate used indicates not less than 47.5 per cent of iodine.

LIPOIODINE-CIBA.—Ethyl diiodobrassidate $C_{21}H_{39}I_2COO(C_2H_5)$, the ethyl ester of diiodobrassidic acid $CH_3.(CH_2)_7.CI:CI.(CH_2)_{11}.COOH$, containing 41 per cent of iodine.

Actions and Uses.—Lipoiodine-Ciba is used as a substitute for the inorganic iodides over which it is claimed to have an advantage in that it is longer retained and therefore better utilized. See preceding article, Iodized Fats and Fatty Acids.

In the form of lipoiodine-Ciba diagnostic, it is used as a contrast medium in the localization of bronchial and pulmonary lesions, as a diagnostic aid in gynecology and myelography, for detecting urethral strictures, and in cavities where intensification of the roentgen ray shadows is desired.

Dosage.—From 0.3 to 0.6 Gm. (5 to 10 grains), or in acute cases from 1.2 to 1.8 Gm. (20 to 30 grains). Lipoiodine-Ciba is supplied in the form of tablets only. The tablets should be masticated before swallowing.

For diagnostic work, from 5 to 20 cc. of lipoiodine-Ciba diagnostic, as determined by the extent of the field to be investigated.

Manufactured by the Society of Chemical Industry in Basle, Switzerland (Ciba Company, Inc., New York). U. S. patent 1,024,171 (April 23, 1912; expires 1929). U. S. trademark 81,554.

Lipoiodine-Ciba Diagnostic: A 60 per cent solution of lipoiodine-Ciba in sesame oil.

Ampules Lipoiodine-Ciba Diagnostic, 5 cc.: Each ampule contains 5 cc. of a 60 per cent solution of lipoiodine-Ciba in sesame oil.

Tablets Lipoiodine-Ciba, 0.3 Gm.

Lipoiodine-Ciba crystallizes in white, odorless and tasteless needles, melting at 37 C. It is insoluble in water, slightly soluble in alcohol, and very soluble in fatty oils, ether and benzene. Lipoiodine-Ciba is decomposed by exposure to direct light.

The iodine content of lipoiodine-Ciba may be determined by the method of H. Baubigny and G. Chavanne (*Compt. rend. Acad. d. sc.*, Paris, **136:** 1197, 1199. *Chem. Zentralbl.* **2:** 69, 1903).

LIPIODOL-LAFAY.—Iodized Poppy-seed Oil 40 per cent.—An iodine addition product of poppy-seed oil containing 39 to 41 per cent of iodine (0.54 Gm. of iodine per cc.) in organic combination.

Actions and Uses.—Lipiodol-Lafay, on account of its high molecular weight, is used as a contrast medium in myelography for detecting urethral strictures, in the spinal column for detecting tumors, and in other conditions for which roentgenologic exploration is desired.

Dosage.—From 1 cc. to 5 cc. (15 to 75 minims) or more according to the uses to which it is to be put.

Manufactured by Andre Guerbet & Cie., Paris (E. Fougera & Co., New York, distributor). No U. S. patent. U. S. trademark 196,499.

Ampoules Lipiodol-Lafay, 1 cc.

Ampoules Lipiodol-Lafay, 2 cc.

Ampoules Lipiodol-Lafay, 3 cc.

Ampoules Lipiodol-Lafay, 5 cc.

Lipiodol-Lafay is a thick, viscous oily liquid, having an alliaceous odor and an oleaginous taste, insoluble in water. On exposure to air and sunlight it decomposes, turning a dark brown color. Specific gravity at 20 C., from 1.340 to 1.350.

Boil 0.5 cc. of lipiodol-Lafay and 10 cc. of alcoholic solution of potassium hydroxide (1 in 10), in a porcelain dish for about five minutes, evaporate the liquid on a water bath and ignite the residue. Dissolve the residue in 10 cc. of water, filter the solution, add 5 cc. of hydrochloric acid to the filtrate, then add chloroform and a few drops of chlorine water and agitate: the chloroform solution is violet. Dissolve 1 cc. of lipiodol-Lafay in 10 cc. of choloroform, add a few drops of phenolphthalein solution and 0.3 cc. of tenth-normal sodium hydroxide solution: the liquid becomes red (*limit of acidity*). Mix 10 cc. of lipiodol-Lafay with 50 cc. of petroleum benzin: a transparent liquid results.

Boil about 1 cc. of lipiodol-Lafay with 10 cc. of nitric acid and 0.5 Gm. of silver nitrate, cool, add 25 cc. of water, collect the precipitate formed on a filter paper, wash free from the excess of silver nitrate; puncture the filter, collect its contents in a glass stoppered flask, treat with 50 cc. of stronger ammonia water, agitate thoroughly and allow to stand for one hour. Filter off the insoluble silver iodide; treat the filtrate with 15 cc. potassium iodide solution, and remove the excess of ammonia by evaporation on a steam bath: no opalescence results (*absence of chlorine compounds*).

Ignite about 1 Gm. accurately weighed: the residue does not exceed 0.01 per cent. Transfer about 0.35 Gm. accurately weighed, to a bomb tube; determine the iodine content by the Carius method: the amount of iodine found is not less than 39 per cent nor more than 41 per cent.

LIPIODOL RADIOLOGIQUE ASCENDANT.—Iodized Poppy-seed Oil 10 per cent.—An iodine addition product of poppy-seed oil containing 9.8 to 11.2 per cent of iodine (0.11 Gm. of iodine per cc.) in organic combination.

Actions and Uses.—In subarachnoid injection for roentgen-ray examination, lipiodol radiologique ascendant is used for recognition of intradural tumors when it is desired to employ a contrast medium of lesser density than that of the spinal fluid.

Dosage.—From 1 to 2 cc., previously brought, with the syringe, to a temperature of 40 C.

Manufactured by Andre Guerbet & Cie., Paris (E. Fougera & Co., New York, distributor). No U. S. patent. U. S. trademark 196,499.

Lipiodol radiologique ascendant is a yellow, oily liquid, having an alliaceous odor and an oleaginous taste, insoluble in water. On exposure to air and sunlight it decomposes, turning a brown color. Specific gravity at 20 C., from 0.99 to 1.00.

Lipiodol radiologique ascendant conforms to the tests for identity and purity, ash and assay as described under lipiodol-Lafay, except that the iodine content found is not less than 9.8 per cent nor more than 11.2 per cent.

LIPIODOL RADIOLOGIQUE DESCENDANT.—Iodized Poppy-seed Oil 35 per cent.—An iodine addition product of poppy-seed oil containing 34 to 36 per cent of iodine (0.45 Gm. of iodine per cc.) in organic combination.

Actions and Uses.—In subarachnoid injection for roentgen-ray examination, lipiodol radiologique descendant is used for the recognition of intradural tumors.

Dosage.—In the normal subject, 2 cc.

Manufactured by Andre Guerbet & Cie., Paris (E. Fougera & Co., New York, distributor). No U. S. patent. U. S. trademark 196,499.

Lipiodol radiologique descendant is a yellow, oily liquid, having an alliaceous odor and an oleaginous taste, insoluble in water. On exposure to air and sunlight it decomposes, turning a dark brown color. Specific gravity at 20 C., from 1.270 to 1.280.

Lipiodol radiologique descendant conforms to the tests for identity and purity, ash and assay as described under lipiodol-Lafay, except that the iodine content found is not less than 34 per cent nor more than 36 per cent.

ORIDINE.—The calcium salt of the iodized fatty acids of cottonseed oil. It contains from 23 to 25 per cent of iodine in organic combination.

Actions and Uses.—Oridine is used as a substitute for the inorganic iodides over which it is claimed to have an advantage in that it is longer retained and therefore better utilized. See preceding article, Iodized Fats and Fatty Acids.

Dosage.—The iodine content of oridine 1 Gm. is approximately equivalent to sodium iodide 0.28 Gm. and to potassium iodide 0.31 Gm. When used for the prophylaxis of goiter, 0.01 to 0.03 Gm. per day are given until 40 doses have been taken.

Manufactured by Eli Lilly and Co., Indianapolis, Ind. No U. S patent. U. S. trademark 185,838.

Oridine Tablets: Each contains oridine, equivalent to iodine 0.01 Gm This dosage form is used only for prophylaxis against goiter and for the treatment of simple goiter.

Oridine is a light brown powder, almost odorless and tasteless. It is almost insoluble in water, benzene, ether and alcohol; slightly soluble in chloroform and carbon tetrachloride.

Mix oridine 1 Gm. with water 20 cc. and filter; the filtrate becomes but slightly opalescent on the addition of silver nitrate solution (*soluble iodides*).

Mix about 0.5 Gm. of oridine, accurately weighed, in a nickel crucible with a mixture of powdered sodium hydroxide 4 parts and potassium nitrate 1 part, and heat until fusion has been completed. Cool and dissolve the fused mass in 150 cc. of water, warming to hasten solution; filter into a 400 cc. beaker and wash well. Add 25 cc. of tenth normal silver nitrate (the amount of silver is "k" in the formula below); then add slowly, with stirring, nitric acid until acid in reaction to litmus paper. Filter the solution through a weighed Gooch crucible, wash and titrate the excess silver nitrate in the filtrate with tenth normal potassium sulpho-cyanate (the amount of silver in the filtrate is "a"). The precipitate in the Gooch crucible (consisting mainly of silver iodide with some silver chloride) is further washed with 3 portions of alcohol, then ether, dried at 100 C. and weighed ("w"). The amount of iodine can be calculated according to the formula

$$x = \frac{.7527\ w + a - k}{293}$$

where w equals combined weight of silver iodide and silver chloride; x equals weight of silver iodide and (w-x) equals weight of silver chloride: by this method oridine contains not less than 23 per cent nor more than 25 per cent of iodine. (Chlorine is used in the manufacture of oridine so that the finished product contains from 1 to 3 per cent of combined chlorine.)

RIODINE.—A 66 per cent solution in oil of an iodine addition product of castor oil. Riodine contains about 17 per cent of iodine.

Actions and Uses.—Riodine is used as a substitute for the inorganic iodides over which it is claimed to have an advantage in that it is longer retained and therefore better utilized. See preceding article, Iodized Fats and Fatty Acids.

Dosage.—From 0.4 to 1.2 Gm. (6 to 18 grains) per day, in capsules, taken after meals. Supplied only in the form of capsules.

Manufactured by P. Astier Laboratories, Paris and New York (Gallia Laboratories, Inc., New York, distributor). No U. S. patent. U. S trademark 86,974.

Riodine Capsules, 0.2 Gm. (3.1 grains).

Riodine is prepared by treating castor oil with hydrogen iodide.

Riodine is an oil-like liquid, light amber in color, having a faint alkaline reaction. It is insoluble in water; soluble in alcohol, chloroform and ether.

When heated, it is decomposed and purple vapors of iodine are given off. When heated with alcoholic potash, riodine is saponified and potassium iodide formed.

STEARODINE. — Calcium Iodostearate. — $Ca[CH_3(CH_2)_7CHI(CH_2)_8CO_2]_2$.—It contains from 26 to 28 per cent of iodine in organic combination.

Actions and Uses.—Stearodine is used as a substitute for the inorganic iodides, over which it is claimed to have an advantage in that it is longer retained and therefore better utilized (See preceding article, Iodized Fats and Fatty Acids).

Dosage.—For prophylaxis of goiter, 0.01 Gm. weekly or biannual series of six weeks' treatment consisting of 0.01 Gm. daily.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

Stearodine Tablets: Each contains stearodine, equivalent to 0.01 Gm. of iodine. This dosage form is used only for prophylaxis against goiter and for the treatment of simple goiter.

Stearodine is a cream colored solid, almost odorless, insoluble in water, soluble in chloroform, ether and benzin.

When stearodine is agitated with diluted nitric acid, the filtrate responds to tests for calcium. When a small quantity of stearodine is warmed with strong sulphuric acid, violet vapors of iodine are evolved.

Agitate about 1 Gm. stearodine with diluted nitric acid: the filtrate is not rendered distinctly turbid by the addition of silver nitrate solution (*absence of inorganic iodide*).

Mix about 0.1 Gm. of stearodine, weighed accurately, with 2 Gm. of sodium hydroxide in a nickel crucible and fuse the mixture gently. Allow the fusion to cool somewhat; add 8 Gm. of fusion mixture (sodium carbonate, potassium carbonate and potassium nitrate) and heat strongly until a clear liquid results. Allow the fusion to cool, dissolve the mass in 250 cc. of water; add 30 cc. sodium hypochlorite solution containing 2.5 per cent available chlorine; after five minutes acidify with an excess of phosphoric acid and heat until all free chlorine has been expelled; add an excess of sodium iodide and titrate the free iodine with tenth normal sodium thiosulphate: each cubic centimeter of tenth normal sodium thiosulphate consumed corresponds to 0.0126 Gm. of iodine; the iodine content found is not less than 26 per cent and not more than 28 per cent.

CALCIUM IODOBEHENATE.—Calioben.—For description see the U. S. Pharmacopeia under Calcii Iodobehenas.

Actions and Uses.—Calcium Iodobehenate is used as a substitute for the inorganic iodides over which it is claimed to have an advantage in that it is longer retained and therefore better utilized. See preceding article, Iodized Fats and Fatty Acids.

Dosage.—From 1 to 3 Gm. (15 to 45 grains) daily.

Sajodin.—Calioben.—A brand of Calcium Iodobehenate-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent 839,509 (Dec. 25, 1906; expired). U. S. trademark 61,730.

Sajodin Tablets, 1 grain.

Sajodin Tablets, 8 grains.

FERRO-SAJODIN.—Ferioben.—Ferro-sajodin is a basic, ferric iodobehenate, approximate formula $Fe(OH)(C_{21}H_{42}ICOO)_2$, which contains at least 5 per cent of iron and at least 24 per cent of iodine.

Actions and Uses.—Ferro-sajodin has the actions of iodides and iron. It is claimed to be more stable and palatable than ferrous iodide, not to injure the teeth or to disturb the gastro-intestinal tract, and that it is free from a constipating tendency. It is claimed that ferro-sajodin is easily absorbed, but that it is slowly eliminated, thus assuring a more prolonged effect than that obtained from inorganic iodides and iron compounds.

Ferro-sajodin is indicated in the conditions in which iron and iodides are employed, such as anemia, rickets, syphilis, chronic bronchitis and arteriosclerosis with anemia.

Dosage.—From 0.5 to 1 Gm. (8 to 15 grains), three times daily. For children from 0.25 to 0.5 Gm. (4 to 8 grains) three times daily. Ferro-sajodin is sold in the form of tablets only. These should be masticated before swallowing or crushed when administered to children.

Manufactured by The Bayer Co., Inc., Rensselaer, N. Y. (Winthrop Chemical Co., Inc., New York, distributor). No U. S. patent. U. S. trademark 61,730.

Ferro-Sajodin Tablets, 8 grains.

Ferro-sajodin is a reddish brown, odorless and tasteless powder; unctuous to the touch; insoluble in water or alcohol; slightly soluble in chloroform, ether and warm fatty oils.

Ferro-sajodin melts to a brownish-black liquid from which iodine vapors are emitted abundantly. Shake about 0.1 Gm. of ferro-sajodin with 5 cc. of chloroform and 5 cc. of diluted hydrochloric acid; allow the acid liquid to separate; decant a portion of it and treat it with an excess of ammonia water. A red precipitate of ferric hydroxide is produced.

Heat about 0.5 Gm. of ferro-sajodin in a reflux apparatus for thirty minutes with 15 cc. of a 15 per cent solution of potassium hydroxide in methyl alcohol; cool and filter, taking care to reserve the filtrate. Treat the residue on the filter with diluted hydrochloric acid and filter. Dilute 1 cc. of the filtrate with 10 cc. of water and add a few drops of potassium ferrocyanide solution: a blue color results. Acidify the reserved alkaline filtrate with dilute sulphuric acid and filter. To a portion of the filtrate, add a few drops of sodium nitrite solution and shake with chloroform: the chloroform layer is colored violet

Mix about 6 Gm. of ferro-sajodin, accurately weighed, with 10 Gm. of anhydrous sodium carbonate; place in a platinum crucible; cover with more of the anhydrous sodium carbonate, and heat slowly until the mixture is melted. Cool, dissolve in water so far as possible, filter and wash the insoluble portion with water. Dissolve the insoluble portion in warm, diluted hydrochloric acid; add 0.5 Gm. of tartaric acid; make alkaline with ammonia water, and add an excess of yellow ammonium sulphide. Allow to stand over night; collect the precipitate; wash it with dilute ammonium sulphide; dissolve it with warm, diluted hydrochloric acid; add an excess of bromine water, followed by an excess of ammonia water; collect the ferric hydroxide, dry it; heat to ferric oxide and weigh in the usual way: the weight of ferric oxide corresponds to not less than 5 per cent of iron.

Boil for one and one-half hours in a reflux apparatus about 3 Gm. of ferro-sajodin, accurately weighed, with 120 cc. of 15 per cent methyl alcohol solution of potassium hydroxide, cool, add 1 Gm. of powdered animal charcoal, and wash into a 500 cc. volumetric flask with water. Filter through a dry filter, rejecting the first portions of the filtrate; treat 250 cc. of the filtrate with sodium acid sulphite solution; acidify with nitric acid, add 40 cc. of tenth-normal solution of silver nitrate, and titrate the excess of silver with tenth-normal solution of potassium sulphocyanate: the silver nitrate consumed corresponds to at least 24 per cent of iodine.

OTHER ORGANIC IODINE COMPOUNDS

IOTHION. — Iopropane. — Diiodohydroxypropane. — 1,3-diiodopropane-2-ol. — $CH_2I.CH(OH).CH_2I$. Iothion contains from 77 to 80 per cent of iodine.

Actions and Uses.—Iothion is used when it is desired to obtain the systemic effect of iodides by external application. Iothion is absorbed from the intact skin. It is claimed to be practically unirritating to the skin in the concentrations ordinarily used, and to produce no discoloration.

Dosage.—Iothion is used in the form of iothion oil, in solution in alcohol or glycerin, or in the form of ointments containing from 5 to 20 per cent of iothion. It is applied without friction, and the parts are not bandaged.

Manufactured by the Bayer Company, Inc., Rensselaer, N. Y. (Winthrop Chemical Company, New York, distributor).

Iothion Oil: Iothion, 10 parts; chloroform, 10 parts; olive oil, 80 parts.

Iothion is a yellowish, oily liquid having a faint but not unpleasant odor. It is insoluble in water; soluble in alcohol, ether, chloroform, carbon disulphide, glycerin and oils. It is volatile at body temperature. It is decomposed by alkalis and weakly alkaline solutions. The specific gravity is from 2.4 to 2.5 at 20 C.

Heat about 1 Gm. of iothion, accurately weighed, on the water bath under a reflux condenser, with 25 cc. of half normal alcoholic potassium hydroxide for from five to six hours. Dilute with water and evaporate the alcohol. Add a slight excess of diluted sulphuric acid and a few cubic centimeters of sodium nitrite solution, and extract with carbon disulphide until all of the iodine has been removed. Titrate the carbon disulphide solution with tenth-normal sodium thiosulphate in the usual way: the tenth normal sodium thiosulphate consumed indicates not less than 77 per cent nor more than 80 per cent of iodine.

IODOXYBENZOATES

Ortho-iodoxybenzoic acid (which contains two oxygen atoms bound to an iodine atom), iodosobenzoic acid (which contains one oxygen atom bound to an iodine atom) and iodobenzoic acid were first prepared by Victor Meyer and co-workers in 1892. Iodoxybenzoic acid resembles salicylic acid, chemically differing in that the hydroxyl group of the latter has been replaced by an iodoxy $\left(\mathrm{I}{=\mathrm{O} \atop =\mathrm{O}}\right)$ group. Chemically, ortho-iodoxybenzoic acid is a strong oxidizing agent; in presence of certain reducing agents it forms iodobenzoic acid, while on addition of alkali to the reducing agent, sodium salicylate may also be formed. In the blood stream its salts are also quickly reduced. Loevenhart and co-workers, who did considerable pharmacologic work (1911-1913), showed that on injection of the salts of iodoxybenzoic acid and iodosobenzoic acid, the hemoglobin was immediately oxidized to oxyhemoglobin. Arkin, who reported its germicidal action against staphylococci, also found later that it stimulated the phagocytosis of streptococci and staphylococci by human leukocytes, and that it stimulated production of hemolysin and agglutinin in rabbits when injected intravenously after immunization. In the meantime Hektoen, following certain immunologic studies, had reported that intravenous injections of sodium iodoxybenzoate produced more antibodies than were present in the control animals. The known actions of the salts of iodoxybenzoic acid, as developed by the foregoing workers, led up to its clinical application by Young and Youmans in the treatment of arthritis. The investigators, in their introduction of the substance, used the sodium salt or ammonium salt prepared extemporaneously; later, they recommended the use of ammonium iodoxybenzoate.

Actions and Uses.—The salts of iodoxybenzoic acid are indicated chiefly in arthritis. Although the salts of iodoxybenzoic acid have benefited patients severely crippled, its use should be largely confined to cases in which permanent anatomic changes have not developed to such an extent as to preclude a reasonable expectation of improvement of function. Should such cases be treated, it should be done with the expectation of employing proper orthopedic procedures subsequently. Patients presenting signs of an active infection are reported to respond best. The salts of iodoxybenzoic acid are reported to be preferably administered intravenously; however, for cases in which the drug cannot be given intravenously, oral administration and administration by high enema have been employed and found effective. Following intravenous injection, fever and chills have been noted, which Young and Youmans regarded as favorable rather than otherwise. These reactions resemble nonspecific protein reactions, though these investigators do not concur in this opinion.

Dosage.—Intravenously, 0.75 to 1 Gm. of the salts of iodoxybenzoic acid is dissolved in 100 cc. of sterile physiologic solution of sodium chloride. It should be administered by the gravity method, over a period of not less than seven or more than twelve minutes, followed by a small amount of the sterile sodium chloride solution, to minimize contact of the drug with the walls of the vein. A course of treatment is from five to ten injections, and the doses may be given twice a week. Orally, the dosage recommended is twice that of the intravenous method; for rectal administration a solution of 2 grams of the ammonium salt has been used.

Caution: Salts of iodoxybenzoic acid are oxidizing substances, and will explode if overheated or exposed to a flame. To avoid slow decomposition, they should also be kept out of direct sunlight, and in a dry place.

AMIODOXYL BENZOATE.—Ammonium *o*-iodoxybenzoate.—$C_6H_4(IO_2)COONH_4$.—The ammonium salt of 2-iodoxybenzoic acid. The latter differs from ortho-hydroxybenzoic acid (salicylic acid) in that the hydroxy group is replaced by the iodoxyl $\left(\mathrm{I}{=\mathrm{O} \atop =\mathrm{O}}\right)$ group. It contains 42.7 per cent of iodine.

Actions and Uses.—See preceding general article, Iodoxybenzoates.

Dosage.—See preceding general article, Iodoxybenzoates.

Amiodoxyl benzoate occurs as a white crystalline, odorless powder, with a slightly bitter taste; readily soluble in water, slightly soluble in alcohol, insoluble in benzene, ether, and most of the other commonly used organic solvents. An aqueous solution (1 in 20) when freshly prepared is colorless, and neutral to litmus.

Dissolve 0.1 Gm. in 5 cc. of water; add an excess of sulphurous acid; collect the resultant iodobenzoic acid on a filter, wash and dry at 105 C.; it melts at 160-162 C. Dissolve 1 Gm. in 20 cc. of cold water and divide in two portions; to one portion add 1 cc. of a neutral potassium iodide solution: 0.1 cc. of tenth-normal sodium thiosulphate solution should completely remove any iodine liberated in five minutes (*uncombined iodoxybenzoic acid*); to the other portion add 2 cc. of acetic acid: there should be no precipitate within five minutes (*iodosobenzoates*). Dissolve 1 Gm. in 50 cc. of water: separate portions of 10 cc. each yield a faint opalescence with 1 cc. of diluted nitric acid and 1 cc. silver nitrate solution (*halides*); a faint turbidity with 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution (*sulphates*); no marked coloration on the addition of 1 cc. ferric chloride solution (*salicylates*). An aqueous solution of the salt meets the requirements of the test for *heavy metals,* U. S. P. X, page 439.

Ignite cautiously about 1 Gm., accurately weighed, *previously* reduced by sulphurous acid in the presence of sulphuric acid: the residue should not exceed 0.1 per cent. Dry about 0.5 Gm., accurately weighed, for forty-eight hours over sulphuric acid in a partial vacuum: the loss in weight should not exceed 1 per cent. Transfer about 0.25 Gm. previously dried to constant weight over sulphuric acid, accurately weighed, to a 500 cc. Erlenmeyer flask, dissolve in 50 cc. of cold water, add 2 Gm. of potassium iodide, followed by 10 cc. of acetic acid, covering with about 150 cc. of cold water, stoppering the flask, and allowing to stand in a cool, dark place for thirty minutes; titrate the liberated iodine with tenth-normal sodium thiosulphate solution, using starch paste as an indicator: the amount of tenth-normal sodium thiosulphate solution consumed corresponds to not less than 10.3 per cent, nor more than 10.8 per cent active oxygen. Transfer about 0.25 Gm., previously dried to constant weight over sulphuric acid, accurately weighed, to a bomb tube; determine the iodine content by the Carius method: the amount of iodine found should not be less than 42 per cent, nor more than 43 per cent.

Amiodoxyl Benzoate-Abbott.—A brand of amiodoxyl benzoate-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

IPECAC PRINCIPLES AND PREPARATIONS

EMETINE BISMUTH IODIDE.—Emetinae Bismutho-Iodidum.—Emetine Bismuthous Iodide.—Bismuth Emetine Iodide.—A complex iodide of emetine and bismuth, containing from 17 to 23 per cent of anhydrous emetine and from 15 to 20 per cent of bismuth.

Actions and Uses.—Emetine bismuth iodide has the action of emetine; but when taken by the mouth, on account of its limited solubility, it is less likely to cause vomiting than the soluble salts of emetine administered by mouth.

It has been used with apparently good results in the treatment of chronic cases and carriers of amebic dysentery, even when the hypodermic administration of emetine had failed.

Dosage.—The commonly used dose has been 0.2 Gm. (3 grains) daily for four days, either in a single dose at the midday meal or in divided doses. The drug should be given as dry powder, enclosed in capsules or cachets as desired, or in the form of pills or capsules which resist disintegration in the stomach.

Emetine bismuth iodide is an odorless, orange-red powder having a slightly bitter taste.

It is but slightly soluble (with decomposition and liberation of emetine) in water, and dilute acids. It is decomposed by alkaline liquids and by strong acids.

Shake 0.1 Gm. of emetine bismuth iodide with 10 cc. of tenth-normal hydrochloric acid during fifteen minutes. Filter and dilute 1 cc. of the filtrate to 100 cc. To a 5 cc. portion add 1 drop of mercuric potassium iodide solution, shake and allow to stand one minute: no distinct milkiness or turbidity should appear.

When assayed by the following method, emetine bismuth iodide contains from 17 to 23 per cent of anhydrous emetine and from 15 to 20 per cent of bismuth.

To about 0.5 Gm., accurately weighed, of emetine bismuth iodide in a glass stoppered flask, add 10 cc. of water and 3 cc. of ammonia water, shake and allow to stand ten minutes. Add 50 cc. of ether to the flask, shake for ten minutes and then shake every ten minutes during two hours. Decant 25 cc. of the ethereal layer into a 25 cc. graduated flask. Filter this through a pledget of cotton into a small beaker. Wash the flask and filter with ether. Allow the ether to evaporate spontaneously and dry over sulphuric acid. Take up the alkaloid with fiftieth-normal sulphuric acid and titrate back with fiftieth-normal sodium hydroxide, using cochineal as an indicator: each cc. of fiftieth-normal sulphuric acid volumetric solution consumed is equivalent to 0.0048 Gm. of anhydrous emetine.

Place the flask, containing the residue from the emetine determination, upon the water bath and allow the remaining ether to evaporate. Transfer the aqueous liquid and precipitate to a beaker, rinsing the flask with a few cubic centimeters of concentrated hydrochloric acid. Add about 30 cc. of concentrated hydrochloric acid to the beaker and boil. Dilute to about 300 cc., again heat to boiling and filter. Add ammonia water until a slight turbidity appears. Add hydrochloric acid drop by drop until the solution just becomes clear. Heat to boiling, add 50 cc. of 10 per cent ammonium phosphate solution and boil for several minutes. Let stand for one-half hour. Transfer the precipitate to a tared Gooch crucible, which has been strongly heated for one hour in a nickel crucible before being weighed. Wash with hot water, dry, and heat in a nickel crucible to constant weight: each gram of bismuth phosphate ($BiPO_4$) corresponds to 0.6863 Gm. of bismuth.

IRON AND IRON COMPOUNDS

Iron is used in medicine: (1) in the form of metallic or elementary iron (reduced iron, U. S. P.); (2) in the ferrous or unoxidized form of combination—responding to tests for ferrous ions (ferrous carbonate in mass of ferrous carbonate and pill of ferrous carbonate, ferrous iodide in syrup of ferrous iodide, U. S. P.); (3) in the trivalent or oxidized form, the ferric compounds—responding to tests for ferric ions (ferric chloride in tincture of ferric chloride, U. S. P.); and (4) complex compounds of iron.

Complex (masked or nonionic) iron compounds are those compounds of iron whose solutions do not respond to the ordinary tests for ferrous or ferric ions because in them the iron is part of a radical. Complex compounds of iron do not have the astringent taste of simple iron solutions. The permanence of these complex radicals differs widely; while some, such as soluble ferric phosphate, U. S. P., and solution of peptonized iron, N. F., are converted to simple ionic iron by action of dilute acids, others resist treatment with strong acids or with alkalis. The complex iron compounds occurring naturally in animal and vegetable tissues (which are often termed food irons) belong generally to the more resistant class, while the complex iron compounds produced artificially are as a rule decomposed rather readily. There is, however, no sharp line of distinction between the natural complex iron compounds and the artificially produced ones, nor is there any good evidence that they differ in therapeutic action. Until a difference in their effects has been demonstrated, we may class together all complex iron compounds whose solutions are not decomposed into simple ionic iron by digestion at body temperature with 0.2 per cent hydrochloric acid and pepsin. (It should be emphasized that salts of iron which give the iron test directly are classed as inorganic iron, whatever their acid radicals may be, and that true iron albuminate and iron peptonate are inorganic iron compounds.)

Actions and Uses.—Solutions of ferric iron are used externally as styptics. Ferric solutions may be used for their astringent effects, internally, and as a gargle. The principal use of iron, however, is in the treatment of anemia and chlorosis. For this purpose, the ferrous salts are usually preferred to the ferric salts, as they are not so caustic and hence are less likely to disturb the stomach. Reduced iron, yielding ferrous chloride when dissolved in the stomach, acts as a ferrous compound, provided the hydrochloric acid in the gastric fluid is sufficient to permit solution. So far as the complex iron compounds are not decomposed by gastric digestion, they also are devoid of gastric effects; but, on the other hand, it has been claimed that certain hemoglobin-like compounds escape absorption altogether. Bunge supposed that only "organic iron" could be absorbed and assimilated by the body, the reputed action of inorganic iron being altogether indirect and due to its local effect on the alimentary canal. This theory was modified by Abderhalden to the effect that inorganic iron, while it could not be converted into hemoglobin, nevertheless, stimulated the conversion of "organic iron." Later work (Tartakowski), however, seems to prove that inorganic iron is assimilated and converted into hemoglobin and thus far is therapeutically fully equal to natural complex iron compounds. Whipple and his co-workers have shown that ferrous carbonate (in the form of Blaud's Pills) aids recovery from the anemia of repeated hemorrhages. A real difference exists between the different iron preparations in their local irritant and astringent action, which is absent in most of the complex iron compounds. These local actions may be desirable in some cases and undesirable in others. This should mainly determine the selection of the particular iron preparation most suitable for each patient. Suitable diet (especially liver, kidney, meat and spinach) is sometimes more effective than the iron preparations, presumably by the cooperation of other factors; for in pernicious anemia, liver extract that is practically iron free is equally active.

Simple Iron Salts

FERROUS LACTATE.—Ferri Lactas.—Iron Lactate.—Ferrum Lacticum.—$Fe(C_3H_5O_3)_2 + 3H_2O$.—The ferrous salt of lactic acid. The salt contains approximately 19 per cent of metallic iron.

Actions and Uses.—Ferrous lactate is a mild chalybeate, which, because of its feeble taste, may be taken without difficulty.

Dosage.—From 0.06 to 1.3 Gm. (1 to 20 grains). Owing to its liability to oxidation, it is best prescribed in solutions containing much sugar. Syrup dissolves 1 Gm. in 120 Gm. (4 grains to the fluidounce).

Ferrous lactate occurs in pale greenish-white crusts, consisting of small needle-shaped crystals or transparent green scales, having a slight, peculiar odor and a sweetish, ferruginous taste. It is slowly soluble in about 40 parts of cold and in 12 parts of boiling water; almost insoluble in alcohol; freely soluble in a solution of an alkali citrate, yielding a green solution. When strongly heated, the salt froths, gives out dense, white, acid fumes, chars and finally leaves a brownish-red residue.

The aqueous solution of the salt has a greenish-yellow color, a slightly acid reaction, and gives a deep blue precipitate with potassium ferricyanide, and a light blue one with potassium ferrocyanide. A 2 per cent aqueous solution of the salt should not yield more than a faint opalescence with a lead acetate solution (*limit or absence of* *sulphate, chloride, citrate, tartrate and malate*). The aqueous solution after acidulation with hydrochloric acid should not yield any precipitate or coloration when treated with hydrogen sulphide (*foreign metals*). The aqueous solution, acidulated with nitric acid, should not afford more than slight opalescence with barium chloride solution or with silver nitrate solution (limit of *sulphate or chloride*). If 25 cc. of a 2 per cent aqueous solution of the salt is mixed with 5 cc. of diluted sulphuric acid, the mixture boiled for a few minutes, an excess of sodium hydroxide solution added and the mixture filtered, the filtrate, when mixed with a few drops of alkaline cupric tartrate solution and boiled, does not yield a red precipitate (*sugar*). If a portion of the salt is triturated with sulphuric acid, no offensive odor is developed (*butyric acid*), nor is any gas evolved (*carbonate*) and the mixture, after standing for some time, does not assume a brown color (*sugar, gum or other readily carbonizable impurities*). If from 1 to 1.5 Gm. of the salt is weighed and moistened with nitric acid and carefully ignited in a porcelain crucible it leaves a residue of ferric oxide, weighing not less than 27 per cent, nor more than 27.8 per cent of the material taken: this residue does not have an alkaline reaction on litmus paper, nor yield anything soluble to water (*foreign salts*).

Iron Lactate-Merck.—A brand of ferrous lactate-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor. No. U. S. patent or trademark.

FERRO-SAJODIN.—See Iodine Compounds, Iodized Fats and Fatty Acids.

Complex Iron Salts

IRON CITRATE GREEN-P. D. & CO.—Iron and Ammonium Citrate Green-P. D. & Co.—A complex ferric ammonium citrate, containing ferric citrate equivalent to 16 per cent of iron (Fe) and ammonium citrate equivalent to 8.1 per cent of ammonia (NH_3).

Actions and Uses.—See preceding article, Iron and Iron Compounds. Iron citrate green-P. D. & Co. is intended for intramuscular and hypodermic administration, it being claimed that because of the higher ammonium citrate content the use of this product is less painful and less liable to produce coagulation of proteins when injected than is produced with the pharmacopeial iron and ammonium citrate.

The Council is not convinced that the intramuscular or hypodermic administration of iron yields effects which differ from those obtained by the oral administration; however, the unsettled state of iron therapy and the rather large clinical use of iron by intramuscular or subcutaneous injection appears to justify the provisional acceptance of this preparation.

Dosage.—From 0.015 (¼ grain) to 0.1 Gm. (1½ grains) administered intramuscularly or subcutaneously. Iron citrate green-P. D. & Co. is marketed in the form of solution only.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

Ampoules Iron Citrate Green-P. D. & Co., ¼ grain: Iron citrate green-P. D. & Co., 0.015 Gm. (¼ grain); quinine and urea hydrochloride, 0.005 Gm.; distilled water, 1 cc.

Ampoules Iron Citrate Green-P. D. & Co., ¾ grain: Iron citrate green-P. D. & Co., 0.05 Gm. (¾ grain); quinine and urea hydrochloride, 0.005 Gm.; distilled water, 1 cc.

Ampoules Iron Citrate Green-P. D. & Co., 1½ grains: Iron citrate green-P. D. & Co., 0.1 Gm. (1½ grains); quinine and urea hydrochloride, 0.005 Gm.; distilled water, 1 cc.

Iron citrate green-P. D. & Co. forms green transparent scales. It is very soluble in water, forming solutions which are stable if protected from light.

Determine the iron content of iron citrate green-P. D. & Co. by the method of the U. S. P. X for iron and ammonium citrate: the iron content is equivalent to 16 per cent. of iron (Fe.). Determine the ammonium content by distillation: it contains ammonium citrate equivalent to 8.1 per cent of ammonia (NH_3).

SOLUBLE FERRIC PYROPHOSPHATE. — For description see the National Formulary under Ferri Pyrophosphas Solubilis.

Maltine Ferrated: Each hundred cc. represents iron pyrophosphate, 1.65 Gm. (8 grains per fluidounce) in maltine (which see under Extract of Malt) as a vehicle.

Manufactured by The Maltine Company, Brooklyn. No U. S. patent. U. S. trademark 44,566.

Complex Iron Salts—Hemoglobin Derivatives

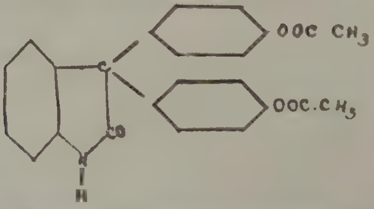
Hemoglobin is the coloring matter of the blood corpuscles and is the most important iron-containing compound of the body. It exists in venous blood as hemoglobin, sometimes called reduced hemoglobin, and in the lungs takes on oxygen in a loose chemical combination becoming oxyhemoglobin.

Hemoglobin is obtained from oxyhemoglobin by the action of various reducing agents.

When ingested, it is decomposed in the stomach, being converted into a protein, globin, and into hematin, an acid, nonalbuminous substance, containing the iron of hemoglobin. The same decomposition is produced by heating in solution to 70 C., and by various chemical agents. It is doubtful whether hemoglobin is absorbed into the blood from the gastro-intestinal canal.

Various preparations of hemoglobin have been put on the market. These are of two classes: (1) preparations consisting essentially of oxyhemoglobin, usually sold under the name "hemoglobin"; (2) preparations derived by the action of reducing agents on the blood, such as zinc and pyrogallol. They consist of reduced hemoglobin or of some modification of it.

ISACEN.—Diacetyldioxyphenylisatin.—



The diacetyl derivative of dihydroxyphenylisatin. The compound resembles phenolphthalein in that the isatin group has somewhat the same general grouping as that of the phthaleins; unlike phenolphthalein, in isacen the two hydroxy radicals (of the two phenol groups) have been condensed with two acetyl groups.

Actions and Uses.—Isacen passes through the stomach unchanged: when it reaches the intestine, a gradual splitting off of dioxyphenylisatin takes place under the influences of the alkaline contents of the intestine. The dioxyphenylisatin thus produced is stated to be nontoxic, not to be absorbed, and to be excreted entirely through the feces: neither dioxyphenylisatin nor the acetyl compound isacen appears in the urine after administration of isacen. Isacen acts as a laxative or purgative, depending on the dosage employed.

Dosage.—As a laxative, 0.005 Gm.; in cases of obstinate constipation, from 0.015 to 0.02 Gm. Isacen is supplied in the form of tablets only.

Manufactured by Hoffmann-LaRoche, Inc., Nutley, N. J. U. S. patent applied for. U. S. trademark 200,220.

Isacen Tablets 0.005 Gm.

Isacen is a white, crystalline, odorless, tasteless powder. It is insoluble in water and dilute hydrochloric acid; slightly soluble in alcohol, very slightly soluble in ether. It melts at 241 to 242 C.

Boil 0.1 Gm. of isacen with 3 cc. of sodium hydroxide solution; cool, dilute to 10 cc. with water: on the addition of a few drops of potassium ferricyanide solution (1 in 10), a cherry red color results. Boil 1 Gm. of isacen with 10 cc. of sodium hydroxide solution; cool, add an excess of diluted sulphuric acid; the odor of acetic acid develops. Dissolve 1 Gm. of isacen in 20 cc. of glacial acetic acid and maintain at 100 C.; a clear solution results (*limit of dioxyphenylisatin*). Boil 1 Gm. of isacen with 50 cc. of distilled water; no odor develops. Cool the solution, add sufficient water to restore the volume of 50 cc.; filter, and to 10 cc. of the filtrate add a few drops of silver nitrate solution; no opalescence is produced immediately (*chloride*). Transfer 2 Gm. of isacen to a glass stoppered cylinder, add 50 cc. of distilled water, shake for five minutes and filter through paper. To 25 cc. of the filtrate add one drop of phenolphthalein solution; on the addition of one drop of tenth-normal sodium hydroxide solution, a pink color results (*limit of acid*). Incinerate about 1 Gm. accurately weighed. The ash should not be more than 0.5 per cent.

LACTIC ACID-PRODUCING ORGANISMS AND PREPARATIONS

During recent years evidence has accumulated which seems to prove that the *Bacillus bulgaricus*, a milk-borne bacillus, cannot be made to grow in the intestinal tract through the administration of living cultures of this organism. On the other hand, evidence has been brought forward to show that the growth in the intestinal tract of the normally present aciduric bacteria may be increased so as to make these the predominating organisms by the administration of milk inoculated and fermented with *B. acidophilus*, by the administration of viable cultures of *B. acidophilus* in conjunction with liberal quantities of lactose or dextrin, or by the administration of these carbohydrates alone. However, *B. acidophilus,* although adapted to intestinal growth by implantation, tends to lose this ability after prolonged cultivation outside the human body. Only comparatively recently isolated cultures should, therefore, be employed in the preparation of products for therapeutic use.

As a result of the considerable amount of favorable evidence, *Bacillus acidophilus* products have come into use in this country. While no one subscribes seriously today to the original theories of Metchnikoff, there are many who believe that the regulation of types of bacteria and of bacterial activities in the intestine may be of much importance. *Bacillus bifidus* and, to a lesser extent, *Bacillus acidophilus,* are common and, as a rule, the predominating types in the intestines of breast-fed infants, and furthermore, the extensive experiments which show these organisms to be of a strictly nonputrefactive and apparently harmless nature may give added weight to the claims made for their therapeutic value.

There is evidence that the administration of sour milk is at times beneficial, particularly in pediatrics, in which field fermented (soured) milks have been used to a considerable extent. Sour milk and sour milk products are used in cases of vomiting, acute diarrrhea, and in chronic disturbances of the gastro-intestinal tract. It is not altogether certain why sour milks are of value, but there is considerable good evidence that the effect is due chiefly to the presence of lactic acid, since milk soured by the addition of pure acid has essentially the same effect as milk soured by bacterial fermentation. A wide clinical observation gives a basis for the opinion that, for certain types of gastric and intestinal disturbances, sour milk accomplishes more than sweet milk with a similar fat, sugar and protein content. No one, of course, will deny the great value of milk, whether sweet or soured by the so-called "lactic acid-producing bacteria," as a growth-promoting and energy-yielding food.

Liquid cultures and aqueous suspensions of acid-producing organisms have been used as local applications to mucous membranes or to arrest putrefaction or suppuration in wounds, abscesses and sinuses. There is no convincing evidence in favor of such use, and it is being generally discontinued.

Sour milk has generally been administered in the form of buttermilk (artificially or naturally soured with *Streptococcus lacticus* predominating) or milk soured with lactic acid-producing organisms such as *Streptococcus lacticus* or *Bacillus bulgaricus* or fermented milks (kefir, kumyss).

To these may now be added the so-called B. acidophilus milk which is prepared by the inoculation of milk which has been previously sterilized or heated for about an hour, at or near boiling temperature, with a pure starter made by inoculating pressure-sterilized milk with viable *B. acidophilus* and incubating at from 35 to 37 C. for from twenty to twenty-four hours. On the completion of proper ripening, which should take place within from twenty to twenty-four hours at from 35 to 37 C., a product is obtained which is slightly sour to the taste and has a characteristic odor not very unlike ordinary pure buttermilk. There is a slight separation of whey, but, on thoroughly mixing, the product has a uniform creamy consistency . According to Kopeloff, storage at icebox temperature rapidly reduces the number of viable organisms in acidophilus milk.

The Council has adopted the following principles to guide in the acceptance of preparations of *B. bulgaricus* and *B. acidophilus:* Bacillus acidophilus milk and broth cultures and concentrates of *B. acidophilus* will be considered acceptable provided the number of viable organisms contained in a stated quantity at the time of sale is declared on the label provided that the label bears an expiration date, and provided that for broth cultures and concentrates the advertising emphasizes the need of coincident administration of carbohydrates (lactose or dextrin). Other preparations of *B. acidophilus,* such as tablets, emulsions and candies, will not be accepted unless adequate evidence is presented that the implantation of *B. acidophilus* may be secured through their use. If such evidence becomes available, these preparations will be accepted under the conditions governing the acceptance of *B. acidophilus* concentrates.

Bacillus bulgaricus preparations may be accepted, provided the claims advanced are limited to recommendations for the preparation of soured milk, and provided no claims for their implantation are made nor any recommendation for their use as external applications are advanced. After 1927, it will be required that each preparation bear on the label a declaration of the number of organisms contained in a given quantity at the time of sale, and that the label contain an expiration date. All lactic acid-producing preparations must be relatively free of foreign organisms.

Bacillus acidophilus (also called *Lactobacillus acidophilus*) and *Bacillus bulgaricus* (also called *Lactobacillus bulgaricus*) belong to a group of bacteria, the lactobacillus group, which has not until recently received much scientific attention, but which is widely distributed in nature. Both are long and fairly slender bacilli, which at times have a tendency to filament formation. They are preferably micro-aerophilic, but grow well under ordinary aerobic conditions. They are gram-positive, though in old cultures individual rods or filaments may at times fail to retain the stain. In spite of claims to the contrary, branching may be observed only occasionally, the branched forms resembling more or less another organism of this group, *Bacillus bifidus,* which quite commonly reveals branching.

Both organisms require carbohydrates for their successful cultivation. Glucose, galactose and lactose broth are fairly suitable, but much less favorable than milk or milk whey. Milk is a particularly good medium for the preservation of viability. For isolation purposes and for colony study, whey-agar and galactose or lactose agar may be used to advantage.

Bacillus acidophilus and *Bacillus bulgaricus* have very many points in common. They differ, however, in the following respects: 1. *B. acidophilus* is relatively slow in acid production in milk, the amount of acid produced during twenty-four hours' incubation rarely exceeding 1 per cent, whereas milk cultures of *B. bulgaricus* may attain an acidity of 3 per cent in the same period of time. 2. Except in the case of so-called border strains, *B. acidophilus* attacks maltose with acid production, while *B. bulgaricus* is unable to do so. 3. *B. acidophilus* is of intestinal origin and, therefore, can adapt itself to intestinal conditions, whereas *B. bulgaricus* is an ordinary saprophyte and is unable to develop or even to maintain itself in the digestive tract. 4. *B. acidophilus* grows at a lower surface tension than does *B. bulgaricus.*

The group of lactobacilli is probably one large group which consists of many varieties in the same way as the *B. coli* and the streptococcus groups. Certain members of the lactobacillus group (acidophilus and bifidus types) are found in the feces of man and animals. Others (bulgaricus type) are very common in cow barns and in dairies, and in the various dairy products. The well-known *Bacillus bulgaricus* is the predominating organism in the oriental sour milk products, and it is to this type of the lactobacillus group that these products in a large measure owe their characteristic properties.

ACIDOPHILUS BACILLUS LIQUID-MULFORD. —A whey culture of *Bacillus acidophilus* (Moro) in a whey medium. It contains 50 million viable organisms per cubic centimeter at the time of sale.

Actions and Uses.—See Lactic Acid Producing Organisms and Preparations, New and Nonofficial Remedies, 1929, p. 220.

Dosage.—One to two tablespoonfuls in a glass of milk or in half a glass of water to which has been added two teaspoonfuls of lactose, three times daily at any time before or two to three hours after a meal.

Manufactured by H. K. Mulford Co., Philadelphia. No U. S. patent or trademark.

BACILLUS ACIDOPHILUS CULTURE (B. A. CULTURE).—A pure aqueous suspension of *Bacillus acidophilus* having an acidity of about 1 per cent lactic acid, marketed in bottles containing about 120 cc. (4 fluidounces). It contains not less than one hundred million viable organisms (*B. acidophilus*) per cubic centimeter at the date of issue.

Actions and Uses. — See preceding article, Lactic Acid-Producing Organisms and Preparations.

Dosage.—From 10 to 15 cc. four times a day, followed by a suitable quantity of lactose.

Manufactured by the B. B. Culture Laboratory, Inc., Yonkers, N. Y. No U. S. patent. U. S. trademark 159,861.

BACILLUS ACIDOPHILUS CULTURE-HOLLISTER-STIER.—A pure culture of *B. acidophilus* in bottles, each containing 200 cc. It contains not less than 150 million viable organisms (*B. acidophilus*) per cubic centimeter at the time of issue.

Actions and Uses.—See Lactic Acid-Producing Organisms and Preparations (New and Nonofficial Remedies, 1929, p. 220).

Dosage.—From 15 to 30 cc. in milk or water to which has been added a suitable quantity of lactose, three times daily. Each bottle bears an expiration date.

Manufactured by the Hollister-Stier Laboratories, Spokane, Wash. No U. S. patent or trademark.

B. ACIDOPHILUS MILK-ADOHR.—A milk culture of *B. acidophilus.* It contains not less than 250 millions of viable organisms *(B. acidophilus)* per cubic centimeter at the time of sale..

Actions and Uses.—See preceding article, Lactic Acid-Producing Organisms and Preparations.

Dosage.—For adults, from 500 to 1,000 cc. daily, the amount to be increased or decreased as required. In some cases the addition of 100 Gm. of lactose daily is recommended, and in rare cases 200 and even 300 Gm. of lactose daily for a week or more. When used in infant feeding it may be diluted with boiled water, it being borne in mind that vitamin C is lacking. B. acidophilus milk-Adohr is marketed in bottles containing 500 cc. and 1,000 cc.; it must be kept cool and should be used prior to the date stamped on the package.

Manufactured by the Laboratory Division of the Adohr Creamery Company, Los Angeles, Calif. No U. S. patent or trademark.

Whole cow's milk is standardized to a fat content of 2 per cent by the addition of fresh skim milk and sterilized at 96 C. for a period of one hour and fifteen minutes on two successive days. After the second heating the milk is cooled to 37 C. and inoculated with a twenty-four hour culture of *B. acidophilus.* After inoculation the milk is kept at 37 C. for from twenty to twenty-four hours until an acidity is reached such that 10 cc. will require for neutralization 8.3 to 9.0 cc. of tneth-normal sodium hydroxide solution, using phenolphthalein as indicator. The product is then agitated until homogeneous, cooled to from 7 to 9 C., and transferred to bottles.

B. ACIDOPHILUS MILK-FAIRCHILD.—A whole milk cultured with *B. acidophilus.* It contains not less than 50 millions of viable organisms *(B. acidophilus)* per cubic centimeter at the time of sale.

Actions and Uses.—See preceding article, Lactic Acid-Producing Organisms and Preparations.

Dosage.—Ordinarily the contents of one bottle (200 cc.) may be taken daily—at one time, or divided as preferred. The quantity may be greatly increased by direction of the physician, especially at the beginning of the treatment when the contents of two or three bottles may be consumed daily. B. acidophilus milk-Fairchild is marketed in bottles containing 200 cc. (7 fluidounces); it must be kept in a cool place and should be used prior to the date stamped on the label.

Manufactured by Fairchild Bros. and Foster, New York. No U. S. patent or trademark.

BACILLUS ACIDOPHILUS MILK-HERMES.—A whole milk cultured with *B. acidophilus.* It contains not less than

200 million of viable organisms (*B. acidophilus*) per cubic centimeter at the time of sale.

Actions and Uses.—See preceding article, Lactic Acid-Producing Organisms and Preparations.

Dosage.—For adults the contents of one bottle (950 cc.) in divided doses daily. To overcome the natural tendency to gas formation at first, it is best to begin with 500 cc. in divided doses and increase to the full dose in two or three days. Lactose may be administered with the milk when indicated. When used for infant feeding, from 250 to 500 cc. of the milk diluted with water that has been boiled and cooled is advised. Bacillus acidophilus milk-Hermes is marketed in bottles containing 950 cc. (1 quart); it must be kept in a cool place and should be used prior to the date stamped on the cap.

Manufactured by the Hermes-Groves Dairy Co., Pittsburgh, Pa. No U. S. patent or trademark.

BACILLUS ACIDOPHILUS MILK-LEDERLE.—Whole milk cultured with *B. acidophilus.* It contains not less than fifty million of viable organisms (*B. acidophilus*) per cubic centimeter.

Actions and Uses.—See preceding article, Lactic Acid-Producing Organisms and Preparations.

Dosage.—For adults, 1,000 cc. of bacillus acidophilus milk-Lederle per day, increased or decreased to meet requirements. When employed in infant feeding, it may be diluted with boiled water. Bacillus acidophilus milk-Lederle must be kept in a cool place and should be used prior to the date stamped on the package.

Manufactured by Lederle Antitoxin Laboratories, New York. No U. S. patent or trademark.

Whole milk is sterilized at 100 C. for 2 hours, cooled to 37 C. and inoculated with a twenty-four hour culture of *B. acidophilus.* After inoculation, the milk is kept at 37 C. for from 20 to 24 hours until an acidity is reached such that 10 cc. will require for neutralization 11 cc. of tenth-normal sodium hydroxide solution, using phenolphthalein solution as indicator. The product is then cooled to 5 C., agitated until homogeneous and transferred to 200 cc. bottles, which are closed with seals. The strain of *B. acidophilus* used is one isolated by Rettger. To insure its adaptability to intestinal implantation, the bacillus is freshly isolated from intestinal contents as frequently as is necessary.

BACILLUS BULGARICUS-SQUIBB.—A pure culture of *Bacillus bulgaricus,* marketed in twelve tubes each containing 12 cc.

Actions and Uses.—Bacillus bulgaricus-Squibb is used for the preparation of fermented (sour) milk. See preceding article, Lactic Acid-Producing Organisms and Preparations.

Manufactured by E. R. Squibb & Sons, New York City. No U. S. patent or trademark.

The culture is grown on whey.

B. B. CULTURE.—A pure culture of *Bacillus bulgaricus,* marketed in bottles containing about 120 cc. (4 fluidounces).

Actions and Uses.—B. B. culture is used for the preparation of fermented (soured) milk. See preceding article, Lactic Acid-Producing Organisms and Preparations.

Manufactured by the B. B. Culture Laboratory, Inc., Yonkers, N. Y. No U. S. patent. U. S. trademark 90,535.

CHEPLIN'S B. ACIDOPHILUS MILK.—A milk culture of *B. acidophilus.* It contains not less than 250 millions of viable organisms *(B. acidophilus)* per cubic centimeter at the time of sale.

Actions and Uses.—See preceding article, Lactic Acid-Producing Organisms and Preparations.

Dosage.—For adults, from 500 to 1,000 cc., increased or decreased to meet individual requirements. When employed in infant feeding, it may be diluted with water which has been boiled and cooled, or with lime water in such proportions as the case may demand but it should be borne in mind that this product does not possess the full growth promoting potency of whole milk; lactose (sugar of milk) should be added to restore the normal sugar content. Cheplin's *B. acidophilus* milk is marketed in bottles containing 400 cc. It must be kept on ice and should be consumed within the period of time stamped on the package (three weeks from date of preparation).

Manufactured by Cheplin Biological Laboratories, Inc., Syracuse, N. Y. No U. S. patent or trademark.

Fresh skimmed cow's milk, standardized with 40 per cent cream so that its final fat content is not less than one-half of 1 per cent, is sterilized in one heating at 120 C. for 15 minutes. After cooling to at least 37 C., the milk is inoculated with a twenty-four-hour culture of pure strains of *B. acidophilus* which have been grown, by repeated transfers, sufficiently long in milk to develop rapidly and bring about proper coagulation of the casein. Viable milk cultures of the organisms are employed as the inoculum. After inoculation the milk is kept at 37 C. for from 20 to 24 hours until an acidity is reached such that 10 cc. will require for neutralization 10 cc. of tenth-normal sodium hydroxide solution, using phenolphthalein as indicator. The product is then agitated until completely homogenous, transferred to 400 cc. bottles, which are closed with seals and cooled to 5 C. The strains of *B. acidophilus* used are isolated by Cheplin. To insure maximum therapeutic effects and colonization within the human alimentary canal, the organism is freshly isolated from human intestinal contents as frequently as is found necessary through actual feeding experiments.

CONCENTRATED CULTURE OF BACILLUS ACIDOPHILUS-P. D. L.—A milk culture of *Bacillus acidophilus* supplied in vials containing 8 cc. It contains not less than 500 million viable organisms *(B. acidophilus)* per cubic centimeter at the time of sale.

Actions and Uses.—See preceding article, Lactic Acid-Producing Organisms and Preparations.

Dosage.—The contents of one vial (8 cc.) daily, to be used either in culturing or incubation of a pint of milk. The culture is sent the patient weekly on the prescription of the physician.

Each package bears an expiration date after which the culture should not be used.

Manufactured by the Physicians Diagnostic Laboratories, Oakland, Calif. **No U. S. patent or trademark.**

CULTURE BACILLUS ACIDOPHILUS-UNITED LABORATORIES.—A pure culture of *B. acidophilus* in bottles, each containing about 120 cc. It contains not less than six hundred millions of viable organisms (*B. acidophilus*) per cubic centimeter at the time of sale.

Actions and Uses.—See preceding article, Lactic Acid-Producing Organisms and Preparations.

Dosage.—15 cc. (4 fluidrachms), diluted with water and followed by a quantity of sugar of milk, twice daily. The culture is distributed by the manufacturer only and is sent by mail. Each bottle bears an expiration date.

Manufactured by United Laboratories, Inc., Pasadena, Calif. No U. S. patent or trademark.

KEFIR FUNGI.—A mixture of bacteria and yeasts capable of causing lactic acid fermentation of milk.

Actions and Uses.—See preceding article, Lactic Acid-Producing Organisms and Preparations.

Dosage.—Kefir kumyss may be prepared by adding active kefir grains to fresh cows' milk, kept at a temperature of from 21 to 27 C. until the effect of fermentation becomes apparent by the rising of the grains to the surface. The grains may then be strained off, and the milk, which then contains sufficient yeast cells to insure continuance of the fermentation, left to itself in well corked bottles.

Kefir occurs in the form of white irregular, slightly round bodies, the size of a walnut, with a very rough, furrowed surfaced, and of a tough, gelatinous consistency. The substance contains *Saccharomyces cerevisiae* (Heyden), *Bacillus acidi lactici* (Hueppe), *Dispora caucasica* (Kern). It acts on milk as follows: Fat, salt and water of the milk remain unaffected. The lactose is gradually decreased and the lactic acid increased. Alcohol is produced along with carbon dioxide; 10 per cent of the casein is converted into acid albumin and peptones, 10 per cent into hemialbumose and the rest loses its lime.

LACTOBACILLUS ACIDOPHILUS MILK (TOWT).—A milk culture of *B. acidophilus.* It contains not less than 250 millions of viable organisms (*B. acidophilus*) per cubic centimeter at the time of sale.

Actions and Uses.—See preceding article, Lactic Acid-Producing Organisms and Preparations.

Dosage.—For adults, from 500 to 1,000 cc. daily, between meals and one hour before retiring. When the administration of lactobacillus acidophilus milk-Towt is to be supplemented by lactose, 50 Gm. is to be administered on the third day, increased to 100, 200, and 300 Gm. on the fourth, fifth, and sixth days, respectively, unless diarrhea occurs or large amounts of gas are formed, when the quantities may be reduced. Lactobacillus acidophilus milk-Towt is marketed in bottles containing 475 cc. (1 pint); it must be kept in a cool place and should be used prior to the date stamped on the package.

Manufactured by the Towt-Nolan Laboratory, Oakland, Calif. No U. S. patent or trademark.

Raw milk containing about 2.5 per cent butter fat is sterilized at 18 pounds pressure for thirty minutes and cooled to 37 C. It is then inoculated with a pure milk culture of *B. acidophilus,* one half of which is the first propagation of the organisms and one half of which is the second propagation. The batch is then incubated at 37 C. for forty-eight hours, at which time it has an acidity of about 0.9 per cent lactic acid and an acidophilus count of about one billion per cubic centimeter. The coagulated curd is thoroughly agitated until it becomes creamy, and is filled into sterile pint bottles through a sterile filling apparatus.

MULFORD ACIDOPHILUS BACILLUS BLOCKS.—A culture of *B. acidophilus* (X and Y strain), embedded in a 2 per cent agar jelly containing milk powder, lactose, *d*-glucose and sucrose, and marketed in the form of chocolate covered cubes, each of which contains approximately 150 billion viable organisms (*B. acidophilus*) at the time of issue.

Actions and Uses.—See preceding article, Lactic Acid-Producing Organisms and Preparations. Evidence was submitted to the Council showing that administration of Mulford acidophilus bacillus blocks is accompanied by a marked decrease in the number of gram-negative *B. coli* types and an increase in the gram-positive *B. acidophilus* types in the feces.

Dosage.—Three to four "blocks" daily, at any time before or two hours after meals. Mulford acidophilus bacillus blocks are marketed in packages of one dozen blocks with a stated expiration date, at which date each block should contain at least 10 billion viable acidophilus bacilli.

Manufactured by H. K. Mulford Co., Philadelphia. U. S. patent 1,540,951 (June 9, 1925; expires 1942). U. S. trademark 205,541.

In the preparation of Mulford acidophilus bacillus blocks a trypsin-digest of milk medium is employed for the propagation of the acidophilus bacilli. This medium is sterilized, cooled to 37 C. and finally inoculated with an eighteen hour old seed-culture of carefully selected strains of *B. acidophilus.* After the proper incubation period (20 hours) at body temperature, the acidophilus bacilli are harvested by centrifugation and the recovered organisms are then suspended in sterile skimmed milk. The acidophilus milk suspension is at once incorporated into a 2 per cent agar base containing milk powder, lactose, *d*-glucose and sucrose; this mixture is allowed to congeal, then is cut into cubes and coated with a high-grade chocolate. The chief function of the chocolate is to protect the agar cube against undue desiccation.

VITALAIT CULTURE BACILLUS ACIDOPHILUS.—A pure culture of *B. acidophilus* in bottles, each containing about 120 cc. It contains not less than eight hundred million viable organisms *(B. acidophilus)* per cubic centimeter at the time of sale.

Actions and Uses.—See preceding article, Lactic Acid-Producing Organisms and Preparations.

Dosage.—15 cc. (4 fluidrachms), diluted with water and followed by a quantity of sugar of milk, twice daily. The culture is distributed by the manufacturer only and is sent by mail. Each bottle bears an expiration date.

Manufactured by The Vitalait Laboratory of California, Pasadena Calif. No U. S. patent or trademark.

LANOLIN.—A name applied to Hydrous Wool Fat-U. S. P. For description see the U. S. Pharmacopeia under Adeps Lanae Hydrosus.

LENIGALLOL. — Pyrogallolis Triacetas. — Triacetylpyrogallol. $C_6H_3(CH_3CO_2)_3$.—Pyrogallol triacetate, obtained by replacing the hydroxyl groups of pyrogallol with acetate groups.

Actions and Uses.—Lenigallol as such is said to be nonpoisonous and nonirritating, but it produces a mild and painless corrosive effect by the gradual liberation of pyrogallol. (See note under Creosote and Guaiacol Compounds.)

It is introduced as a substitute for pyrogallol in psoriasis, lupus, acute and subacute eczema of children and other skin diseases.

Dosage.—In 5 to 10 per cent ointment, usually with zinc oxide.

Manufactured by Knoll A.-G., Ludwigshafen a.Rh., Germany (E. Bilhuber, Inc., New York, distributor). No U. S. patent or trademark.

Leningallol-Zinc Ointment' It contains lenigallol 6 per cent in a base composed of zinc oxide ointment-U. S. P.

Lenigallol is prepared by boiling 10 parts of pyrogallol, 1 part sodium acetate and 25 parts of acetic anhydride for two hours, and washing the crystalline product on a filter with water.

It is a white, crystalline powder, melting at 165 C. It is insoluble in water, but soluble with decomposition in warm aqueous alkalies.

Lenigallol is incompatible with alkalis, strong acids and oxidizing agents.

LIQUID PETROLATUM. — Petrolatum Liquidum. — For description see the U. S. Pharmacopeia or Useful Drugs.

Actions, Uses and Dosage.—See Useful Drugs.

Abbott's Mineral Oil Emulsion.—Liquid petrolatum, 40 cc.; agar, tragacanth and gelatin, 2 Gm.; sugar and flavoring, 2 Gm., and water sufficient to make 100 cc.

Prepared by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

Petrolagar: Liquid petrolatum 65 cc., emulsified with agar in a menstruum containing sugar, flavoring, sodium benzoate 0.1 Gm., and water to make 100 cc.

Prepared by the Petrolagar Laboratories, Inc., Chicago. No U. S. patent U. S. trademark 165,616.

Petrolagar (Unsweetened): Liquid petrolatum 65 cc., emulsified with agar in a menstruum containing sodium benzoate 0.1 Gm., and water to make 100 cc.

Prepared by the Petrolagar Laboratories, Inc., Chicago. No U. S. patent U. S. trademark 165,616.

Petrolagar (with Milk of Magnesia): Liquid petrolatum, 65 cc.; magnesia magma, 8 cc.; emulsified with agar in a menstruum containing sugar, flavoring, sodium benzoate 0.1 Gm., and water to make 100 cc.

Prepared by the Petrolagar Laboratories, Inc., Chicago. No U. S. patent. U. S. trademark 165,616.

Petrolagar (with Phenolphthalein): Liquid petrolatum 65 cc., emulsified with agar in a menstruum containing phenolphthalein 0.32 Gm., sugar, flavoring, sodium benzoate 0.1 Gm., and water to make 100 cc.

Prepared by the Petrolagar Laboratories, Inc., Chicago. No U. S. patent U. S. trademark 165,616.

Squibb's Liquid Petrolatum with Agar: Liquid petrolatum-Squibb, heavy (California), 50 cc.; agar, 1.5 Gm.; sodium benzoate, 0.1 Gm.; acacia, glycerin and water sufficient to make 100 cc.

Prepared by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

LITHIUM SALTS

The lithium ion acts as a depressant on the heart, but less so than the potassium ion. It acts as a gastric and intestinal irritant, and disturbances of the alimentary tract have been produced by the administration of lithium salts. While lithium bromide, lithium iodide and lithium citrate have had some vogue in medicine, these salts possess no advantage over the corresponding potassium or sodium salts and have been practically abandoned. Owing to the citrate radical, lithium citrate, like the citrates of sodium, potassium, calcium, etc., has some diuretic action which depends on its conversion to carbonate in the body with its consequent tendency to decrease the acidity of the urine. The use of lithium salts as uric acid solvents was based on a misconception of chemical facts. There is no reliable clinical evidence that lithium salts increase the excretion of uric acid by the kidney except possibly through a diuretic action; and this is not superior to that of corresponding potassium or sodium salts. Experimental work has failed to show that lithium salts cause the absorption of deposited urates in gouty tophi.

LIVER PREPARATIONS

Recent investigation has demonstrated striking therapeutic effects from the feeding of liver or certain preparations of liver in pernicious anemia. Minot and Murphy (J. A. M. A. **89**:759 [Sept. 3] 1927) report the response to the feeding of liver to be reflected in the peripheral blood by a temporary increase in the number of reticulated red blood corpuscles, followed by a marked rise in the total number of erythrocytes and in the concentration of hemoglobin. To avoid the inconvenience of administering large amounts of liver, investigators have searched for effective concentrates. The work of Minot and Murphy (opp. cit.) and of Koessler and Maurer (J. A. M. A. **89**:759 [Sept. 3] 1927) has demonstrated the effectiveness of such concentrates when used in combination with adequate diets.

The administration of liver or liver preparations in other forms of anemia has been proposed, but the conditions in which it may be of value are not yet determined. Preparations obtained from liver have also been used experimentally as a means of controlling essential hypertension and in certain eclamptic conditions. Thus far the Council has accepted only preparations intended for the treatment of pernicious anemia.

CONCENTRATED LIVER EXTRACT-ARMOUR.—A solution of a water-soluble fraction extracted from fresh mammalian liver. One hundred cc. represents fresh liver, 767 Gm. (1 fluidounce represents 8 ounces avoirdupois).

Actions and Uses.—Concentrated liver extract-Armour is used in the treatment of pernicious anemia. Its value in other types of anemia has not been established.

Dosage.—Concentrated liver extract-Armour is administered orally. The average dose is 15 cc. (4 fluidrachms) three times daily, mixed with orange juice or milk.

Manufactured by Armour and Company, Chicago. No U. S. patent or trademark.

Concentrated liver extract-Armour is made by the process developed by Dr. K. K. Koessler and his co-workers, Drs. M. T. Hanke and Siegfried Maurer in the laboratory of the Otho S. A. Sprague Memorial Institute at the University of Chicago. Fresh livers still retaining the animal heat are finely minced and macerated with three volumes of water. The coagulable proteins are removed by heat and the liquid is condensed at low temperature and negative pressure. The resulting extract is treated with hot 85 per cent alcohol under a reflux condenser and the soluble fraction separated by filtration. The clear filtrate is evaporated to dryness in vacuo and the residual extract dissolved in sufficient distilled water containing 20 per cent of alcohol so that 100 cc. represents 767 Gm. of fresh liver.

LIVER EXTRACT NO. 343.—A water-soluble, nitrogenous, nonprotein fraction obtained from fresh mammalian liver. It is supplied in vials containing an amount of powdered extract (3 to 4 Gm.) representing 100 Gm. of fresh liver.

Actions and Uses.—Liver extract No. 343 is used in the treatment of pernicious anemia. Only preliminary observations have been made concerning its value in conditions other than pernicious anemia; apparently it is of value in some other types of anemia, but definitely seems to be of little or no value in many cases of ordinary secondary anemia.

Dosage.--Liver extract No. 343 is administered orally, the contents of one vial being dissolved in about 30 cc. (1 fluidounce) of water, orange juice or other vehicle. Exact knowledge concerning the daily dose is yet to be determined. Many patients have improved promptly while taking daily the contents of three vials of liver extract No. 343, but as a rule not so rapidly as other patients taking double this amount. The optimum daily dosage appears to be the contents of from six to eight vials. Very large amounts have been given for some days without causing untoward consequences, but may possibly stimulate the blood-forming organs to an undesirable degree.

It may be advisable to give daily to very sick patients the contents of eight vials for the first ten days, after which time the amount may be reduced. As an initial daily dose for the average case, the contents of three to six vials is proposed. This amount is to be taken until the number of red blood cells returns to normal. The maintenance dose required has not yet been determined, but it appears that the use of the extract (or of liver) must be continued to prevent relapse. For the present it is advised that the contents of two or three vials be taken daily and that the patient and his blood be examined at intervals of a month so that the maintenance dose required by the patient may be determined.

Manufactured by Eli Lilly & Company, Indianapolis, under direction of the Committee on Pernicious Anemia of the Harvard Medical School. No U. S. patent or trademark.

To prepare liver extract No. 343, livers from edible animals are ground directly into water, and the mixture adjusted to the isoelectric point (approximately *p*H 5 to *p*H 6). The mixture is then heated to coagulate protein (approximately 80 C.); stirred for thirty minutes, and filtered. The filtrate is reduced in vacuum to a small volume and enough 95 per cent alcohol added to produce a concentration of 70 per cent. The precipitate which is formed is discarded and the filtrate reduced to a small volume; added to absolute alcohol and the precipitate separated, dried in vacuum and powdered.

Liver extract No. 343 is a yellow powder having a not unpleasant taste, almost entirely soluble in water. It is precipitated from the aqueous solution by alcohol and acetone. It is insoluble in ether.

MANGANESE COMPOUNDS

Depending on their oxidizing power, permaganates—potassium permanganate, U. S. P., and zinc permanganate, N. N. R. —are used as germicides and disinfectants as well as for their styptic action. Compounds of manganese, particularly manganese dioxide (precipitated manganese dioxide, U. S. P.), have been used for systemic effects, especially as emmenagogues; but the evidence for their usefulness is not very convincing.

The use of manganese dioxide as an emmenagogue is highly recommended by some authors on the supposition that it increases the flow of the blood to the pelvic organs. Since manganese is but very little absorbed, and in the form of the insoluble oxide can have very little local action, it is difficult to conceive how it could produce this effect. It has been claimed that manganese is a normal constituent of human blood, but the researches of Bertrand and Medigreceanu have shown the amount to be extremely small, not exceeding 0.05 mg. per liter.

Compounds of manganese have been used, either as substitutes for, or in combination with, iron, in the treatment of anemia, chlorosis. Since manganese is slightly absorbed, it is possible that it promotes the formation of hemoglobin.

However, in spite of the many years of its trial, no acceptable evidence has been brought forward to show that the administration of manganese compounds has a favorable effect on blood formation.

ZINC PERMANGANATE.—See Zinc Compounds.

MEDICINAL FOODS

Medicinal foods are preparations of alimentary substances especially adapted for dietotherapy or designed to supply special needs in the nutrition of the sick. The estimations of the nutritive values of these medicinal foods are here based on the calorific values of their carbohydrate, fat and protein contents, and do not include the calorific values of any alcohol or glycerol that they may contain. In the computation of the calorific values, the following factors are used as the equivalents in large calories of 1 Gm. of foodstuff: for carbohydrate, 4.1; for fat, 9.2; for protein, 4.1. The protein content of these foods has generally been estimated by multiplying the nitrogen content by 6.25. It is not, however, conceded that all of the nitrogen represents nutritional nitrogenous matter. Medicinal foods may be divided, for convenience, into the following classes: protein foods, carbohydrate foods, non-nutritive foods, vitamin-rich foods, modified milk products and diabetic foods.

Protein Foods

Actions and Uses: Dry protein, predigested or not, may be used to increase the protein content of soups, gruels and other liquid foods. The predigestion of protein may be of value in conditions in which the digestive power of the stomach is lacking. In such cases meat fiber fails of digestion and may be irritating to the intestine. Predigested protein may also be of value for use in rectal alimentation. Food rich in protein is also employed in the treatment of conditions in which it is desired to give a diet having a low carbohydrate content and in the treatment of which protein is not contraindicated.

Dosage: The dosage of dry protein is determined by the tolerance of the patient and by his nutritive needs. Each Gram of dry protein yields about 4.1 calories.

The dry proteins are presented in the following principal forms: meat, predigested and in the form of a dry powder; casein, usually rendered more soluble by partial conversion to sodium caseinate; legumes, such as flour made from the soy bean; cereal flours containing a high proportion of protein; mixtures containing dried protein mixed with other nutrients.

CALCIUM CASEINATE.—Calcii Caseinas.—Casein from cow's milk rendered partially soluble by combination with calcium, and containing not less than 1.4 per cent nor more than 2.1 per cent of calcium.

Actions and Uses.—The diarrheal diseases of infancy are now generally treated by dietetic measures. A useful food may be made from the curd of milk (casein) and diluted milk, the resultant mixture containing a moderate amount of fat, a small amount of sugar and a large amount of protein (casein) and salts, particularly salts of calcium. To obtain such a food a mixture of calcium caseinate and diluted milk is used.

Dosage.—For infants and children, calcium caseinate is administered in a mixture of milk and water or milk and gruel, approximately 10 Gm. (⅓ oz.) being used in 500 cc. (1 pint) of solution, and the mixture boiled. For adults, it may be mixed with milk, skimmed milk or buttermilk in the proportions of 20 Gm. (⅔ oz.) to 1,000 cc. (1 quart) of diluent.

Calcium caseinate is a yellowish white, fluffy powder; free from "sour" or rancid odor, and having a characteristic, slightly saline taste; permanent in the air.

On agitation with warm water, calcium caseinate partially dissolves, forming a pseudo-solution or turbid suspension; insoluble in alcohol, ether or chloroform. The aqueous solution of calcium caseinate has a neutral or faintly alkaline reaction to phenolphthalein. The solution gives the biuret reaction and is precipitated by acids and by concentrated solutions of many salts.

If incinerated, calcium caseinate emits an odor characteristic of burning protein and leaves a residue consisting chiefly of calcium pyrophosphate.

Weigh accurately from 1 to 2 Gm. of calcium caseinate, heat in a silica dish until the material is charred and most of the carbon is consumed. Digest the residue with dilute hydrochloric acid; filter, dry the filter, ignite it and repeat the extraction with hydrochloric acid. Unite the acid extracts and make up the solution to 100 cc. To 50 cc. of the solution, add 1 cc. of concentrated sulphuric acid and heat to boiling. Add 100 cc. of alcohol, stir well and allow to stand over night. Collect the precipitate in a weighed Gooch crucible, wash it with alcohol until free from acid, dry it at 120 C. and weigh as anhydrous calcium sulphate, $CaSO_4$: the weight should correspond to from 1.4 to 2.1 per cent of calcium, equivalent to from 2 to 3 per cent of calcium oxide. To 25 cc. of the solution of the ash add sufficient ammonium hydroxide to render neutral, add 2 cc. of concentrated nitric acid and 2 Gm. of ammonium nitrate, heat nearly to boiling and add an excess of ammonium molybdate solution. Allow to stand over night, collect the precipitate on a filter, dissolve it in a small quantity of ammonia water, add an excess of magnesia mixture, allow to stand over night, collect in a weighed Gooch crucible, dry and heat to magnesium pyrophosphate in the usual way and weigh: the weight corresponds to not less than 0.6 per cent of phosphorus, equivalent to not less than 1.35 per cent of phosphorus pentoxide (P_2O_5).

Weigh accurately from 1 to 2 Gm. of calcium caseinate and dry it to constant weight at 100 C.: the loss does not exceed 10 per cent (*limit of moisture*).

Add 10 cc. of water to about 1 Gm. of calcium caseinate, accurately weighed. Mix thoroughly with a glass rod and allow to stand for 15 minutes. Transfer to a Rohrig tube or a separator with 10 cc. of ammonia-alcohol (1 volume of stronger amonia water and 4 volumes of alcohol). Mix thoroughly, add 25 cc. of ether, shake thoroughly for half a minute, add 25 cc. of petroleum ether and shake again for half a minute. Allow to stand for about 20 minutes or until the liquids have separated. Draw off the ether solution as completely as possible, filtering through a pledget of cotton into a weighed flask. Repeat the extraction with ether and petroleum ether, using 15 cc. of each solvent. Evaporate the combined extracts and dry the residue at 100 C. to constant weight: the residue corresponds to not more than 2.5 per cent of the weight taken (*limit of fat*).

Determine the nitrogen in a weighed quantity of calcium caseinate by the Kjeldahl method: the nitrogen corresponds to not less than 12.6 per cent of the weight taken.

Casec.—A brand of calcium caseinate-N. N. R.

Manufactured by Mead Johnson and Company, Evansville, Ind. No U. S. patent. U. S. trademark 149,683.

Larosan-Roche.—Stoeltzner's Casein Calcium.—A brand of calcium caseinate, containing 1.75 per cent of calcium.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J.). U. S. patent 1,087,515 (February, 1914; expires 1931). U. S. trademark 94,282.

Larosan-Roche is prepared by treating a suspension of casein in water with calcium hydroxide in such quantities as to yield a solution neutral to phenolphthalein, and then evaporating the solution to dryness in a special apparatus.

Protolac.—A brand of calcium caseinate-N. N. R.

Manufactured by the Dry Milk Company, New York. U. S. patent 1,412,462 (April 11, 1922; expires 1939). U. S. trademark 145,077.

CASEIN.—Caseinas.—The protein separated from milk by the action of acids or enzymes and purified. It contains not less than 15 per cent of nitrogen, calculated on the moisture-free material.

Actions and Uses.—Casein is used as a food, being added to other ingredients of the diet when it is desired to increase the content of protein in the diet. This occurs occasionally in the feeding of infants, in the nutrition of adult convalescents, and undernourished persons, and in the dietotherapy of diabetes. Casein is readily digested, furnishes phosphorus in addition to the usual amino-acid derivatives of proteins, and represents a protein of good nutritional quality. Casein is also used in the preparation of special foods for diabetics or others for whom a regimen poor in carbohydrate or fat may be desired.

Dosage.—The quantities which may be desirable to use vary widely in accord with the purpose of the feeding. Hence the dosage cannot be designated in definite terms.

Casein is soluble in ammonia water and in aqueous solutions of the fixed alkali hydroxides; insoluble in water, alcohol, ether, chloroform, or benzene. A suspension of casein in water slightly reddens blue litmus paper, but casein has both acid and basic properties.

Char about 2 Gm. of casein, accurately weighed, extract with hot water, using 5 successive portions of about 10 cc. each, dry the insoluble portion, heat it to obtain a white or gray ash (moistening with nitric acid if necessary), add the aqueous extract, evaporate the mixture, heat the residue, and weigh: the ash does not exceed 2 per cent of the weight taken.

Weigh accurately from 1 to 2 Gm. of casein and dry it in an air oven at 100 C. to constant weight: the loss does not exceed 10 per cent.

Add 10 cc. of water to about 1 Gm. of casein, accurately weighed. Mix thoroughly with a glass rod and allow to stand for 15 minutes. Transfer to a Rohrig tube or a separator with 10 cc. of ammonia-alcohol (1 volume of stronger ammonia water and 4 volumes of alcohol). Mix thoroughly to completely dissolve the casein. Add 25 cc. of ether, shake thoroughly for half a minute, add 25 cc. of petroleum ether and shake again for half a minute. Allow to stand for about 20 minutes or until the liquids have separated. Draw off the ether solution as completely as possible, filtering through a pledget of cotton into a weighed flask. Repeat the extraction with ether and petroleum ether, using 15 cc. of each solvent. Evaporate the combined extracts and dry the residue at 100 C. to constant weight: the residue corresponds to not more than 1 per cent of the weight taken.

Determine the nitrogen in a weighed quantity of casein by the Kjeldahl method: the nitrogen corresponds to not less than 15 per cent of the moisture-free material.

CELLU SOY BEAN FLOUR.—A partially defatted flour prepared from the soy bean, having approximately the following composition: protein, 45.5; carbohydrate, 25.5, of which less than one half readily yields sugar; fat, 8.5; ash, 6.0; fiber, 4.7; and water, 9.5.

Actions and Uses.—Cellu soy bean flour may be used for preparing bread and muffins. It is indicated in cases in which a diet relatively free from carbohydrate is desired, as in diabetes and amylaceous dyspepsia. It has also been suggested for use in the diet in obesity. The nutritive value of 500 Gm. of this flour corresponds approximately to 1,845 calories, of which 932 are yielded by protein, 522 by carbohydrate, and 391 by fat.

Manufactured by The Chicago Dietetic Supply House, Chicago. No U. S. patent. U. S. trademark 133,954.

Cellu Soy Crisp.—A prepared "breakfast food" made from cooked soy beans without removal of fat and having approximately the following composition: protein, 45.6; carbohydrate, 16.1, of which less than one half readily yields sugar; fat, 20.8; ash, 6.7; fiber, 6.8; and water, 4.0.

Cellu soy bean flour is made by grinding whole soy beans and expressing some of the fat.

CURDOLAC CASEIN-BRAN IMPROVED FLOUR.—A flour prepared from casein, carbohydrate-free bran, and soya bean, to which leavening and flavoring have been added, having approximately the following composition: protein, 38 per cent; fat, 9 per cent; carbohydrate, 4.5 per cent; other nitrogen-free extract (by difference), 36.99 per cent; fiber, 6.53 per cent; ash, 7.78 per cent; moisture, 4.98 per cent.

Actions and Uses.—Curdolac casein-bran improved flour may be used for the preparation of muffins or bread having a relatively low carbohydrate content and low food value, with bulk. The nutritive value of 500 Gm. corresponds approximately to 1,285 calories, of which 779 are yielded by protein, 414 by fat, and 92.2 by carbohydrate.

Manufactured by the Curdolac Food Company, Waukesha, Wis. No U. S. patent. U. S. trademark 145,646.

CURDOLAC SOYA-BRAN FLOUR.—A flour prepared from soya bean and a starch-free bran with a leavening mixture, having the following approximate composition: protein, 27.31

per cent; fat, 15.70 per cent; carbohydrate, 7 per cent; other nitrogen-free extract (by difference), 23.68 per cent; fiber, 8.92 per cent; moisture, 4.61 per cent; ash, 12.70 per cent.

Actions and Uses.—Curdolac soya-bran flour may be used for the preparation of bread and muffins for use in diets in which a comparatively low carbohydrate content is desired. The nutritive value of 500 Gm. corresponds approximately to 1,195 calories, of which 355 are yielded by protein, 722 by fat, and 14 by carbohydrate.

Manufactured by the Curdolac Food Company, Waukesha, Wis. No U. S. patent. U. S. trademark 145,646.

CURDOLAC BREAKFAST CEREAL.—A medicinal food prepared from soya beans blended with wheat products, including starch-free bran, having the following approximate composition: protein, 25.99 per cent; fat, 10 per cent; carbohydrate, 14.9 per cent; nitrogen-free extract (by difference), 24.04 per cent; fiber, 8.68 per cent; moisture, 3.94 per cent; ash, 12.40 per cent.

Action and Uses.—Curdolac breakfast cereal may be used as a hot food in diets in which a comparatively low carbohydrate content is desired. The nutritive value of 500 Gm. corresponds approximately to 1,297 calories, of which 532 are yielded by protein, 460 by fat, and 305 by carbohydrate.

Manufactured by the Curdolac Food Company, Waukesha, Wis. No U. S. patent. U. S. trademark 145,646.

CURDOLAC CASEIN COMPOUND.—A flour prepared from casein, vegetable fiber and a leavening mixture to which sodium chloride and gluside (0.00313 per cent) are added, having approximately the following composition: protein, 42.7 per cent; fat, 0.75 per cent; nitrogen-free extract (by difference), 42.35 per cent; ash, 5.6 per cent; moisture, 5.23 per cent; fiber, 3.36 per cent.

Actions and Uses.—Curdolac casein compound may be used for the preparation of carbohydrate-free bread, muffins, cake, etc., for use in diets in which a relatively low carbohydrate content is desired. The nutritive value of 500 Gm. corresponds approximately to 909 calories, of which 875 are yielded by protein and 34 by fat.

Manufactured by the Curdolac Food Company, Waukesha, Wis. No U. S. patent. U. S. trademark 145,646.

CURDOLAC SOYA FLOUR.—A flour prepared from the soy bean, having approximately the following composition: protein, 42 per cent; fat, 18 per cent; nitrogen-free extract, 22.04 per cent, of which less than 0.10 per cent yields carbohydrate in assimilable form; crude fiber, 7.86 per cent; ash, 4.1 per cent; water, 6 per cent.

Actions and Uses.—Curdolac soya flour may be used for the preparation of foods in diets in which a relatively low carbohydrate content is desired. The nutritive value of 500 Gm.

corresponds approximately to 1,709 calories, of which 861 are yielded by protein, 828 by fat, and 20 by assimilable carbohydrate.

Manufactured by the Curdolac Food Company, Waukesha, Wis. No U. S. patent. U. S. trademark 145,646.

CURDOLAC WHEAT-SOYA FLOUR.—A flour prepared from soya beans, starch-free bran and a small proportion of wheat, with leavening and flavoring, having approximately the following composition: protein, 23 per cent; fat, 9.3 per cent; carbohydrate, 20.5 per cent; other nitrogen-free extract (by difference), 23.86 per cent; fiber, 6.02 per cent; moisture, 5.52 per cent; ash, 11.8 per cent.

Actions and Uses.—Curdolac wheat-soya flour may be used for the preparation of muffins, cakes, waffles, etc., of well balanced food value for use in restricted diets. The nutritive value of 500 Gm. corresponds approximately to 1,318 calories, of which 471 are yielded by protein; 427 by fat, and 420 by carbohydrate.

Manufactured by the Curdolac Food Company, Waukesha, Wis. No U. S. patent. U. S. trademark 145,646.

CURDOLAC SOYA-CEREAL JOHNNY CAKE FLOUR.—A flour prepared from soya beans and cereal products, to which leavening and flavoring have been added, having approximately the following composition: protein, 35.25 per cent; fat, 16.3 per cent; carbohydrate, 20 per cent; other nitrogen-free extract (by difference), 10.52 per cent; fiber, 6.22 per cent; moisture, 6.58 per cent; ash, 5.13 per cent.

Actions and Uses.—Curdolac soya-cereal johnny cake flour may be used in the preparation of muffins, cakes, waffles, etc., for use in diets relatively low in carbohydrate, designed for those who cannot use products made with bran. The nutritive value of 500 Gm. corresponds approximately to 1,901 calories, of which 722 are yielded by protein, 769 by fat, and 410 by carbohydrate.

Manufactured by the Curdolac Food Company, Waukesha, Wis. No U. S. patent. U. S. trademark 145,646.

CURDOLAC SOYA-BRAN BREAKFAST FOOD.—A medicinal food prepared from soya beans and a starch-free bran, to which has been added leavening, flavoring, gluside (0.0225 grains to the ounce), and oils without food value, having approximately the following composition: protein, 15.19 per cent; fat, 5.26 per cent; available carbohydrate, 1.3 per cent; other nitrogen-free extract (by difference), 50.39 per cent; fiber, 17.8 per cent; moisture, 2 per cent; gluside, 0.0006 per cent.

Actions and Uses.—Curdolac soya-bran breakfast food may be used in diets in which a low carbohydrate content is desired. The nutritive value of 500 Gm. corresponds approximately to 565 calories, of which 303 are yielded by protein, 236.7 by fat, and 26 by carbohydrate.

Manufactured by the Curdolac Food Company, Waukesha, Wis. No U. S. patent. U. S. trademark 145,646.

DRY PEPTONOIDS.—A medicinal food prepared from beef, milk and wheat, containing 40 per cent of protein and 51.5 per cent of carbohydrate.

Actions and Uses.—See preceding article, Protein Foods. The nutritive value of 500 Gm. of dry peptonoids corresponds approximately to 1,876 calories, of which 820 are produced by protein and 1,056 by carbohydrate. The largest dose usually given (16 Gm.), is, therefore, equivalent to about 60 calories.

Dosage.—For an adult, from 8 to 16 Gm. (¼ to ½ ounce), taken in water, milk, wine, broths, soups, etc.; also in gruels, in which case it should first be dissolved in a small quantity of water.

Manufactured by the Arlington Chemical Co., Yonkers, N. Y. U. S. trademark, Oct. 17, 1882.

Dry peptonoids is said to be made from beef, milk and wheat, by digesting the protein with pepsin and pancreatin and the carbohydrates with pancreatin and malt diastase. The resultant solutions are assayed, mixed in proper proportions, and, the acid used in the digestion having been neutralized, the mixture concentrated in vacuo, the residue sterilized, dried and brought to uniform composition by the addition of milk sugar.

It consists of light brown granules of pleasant odor and taste. It is very soluble in water.

DIOPROTEIN PREPARED CASEIN FLOUR.—Casein to which has been added 4 per cent of a leavening mixture composed of sodium bicarbonate, monocalcium phosphate and sodium aluminum sulphate.

Actions and Uses.—This flour is employed in cases such as diabetes, in which carbohydrate is contraindicated.

Dosage.—Dioprotein prepared casein flour is adapted for the preparation of bread, cake, muffins, biscuits, etc.

Manufactured by The John Norton Company, Columbus. No U. S. patent or trademark.

HEPCO FLOUR.—A flour prepared from the soy bean, having approximately the following composition: protein, 42.9; carbohydrate, 22.4, of which less than one-half readily yields sugar; fat, 20.8; ash, 5.1; fiber, 4.2, and water, 4.6.

Actions and Uses.—It is claimed that clinical trials have shown that the carbohydrate in hepco flour is, in the main, not sugar producing and that therefore hepco flour is a suitable food material in cases in which carbohydrate is contraindicated, as diabetes and amylaceous dyspepsia. It has also been suggested for use in the diet in obesity. The nutritive value of 500 Gm. of this flour corresponds approximately to 2,300 calories, of which 880 are yielded by protein, 460 by carbohydrate (on the assumption that all the carbohydrate is utilized), and 960 by fat.

Manufactured by Waukesha Health Products Company, Waukesha, Wis. No U. S. patent. U. S. trademark 103,772.

Hepco Dodgers.—A biscuit prepared from and having approximately the same composition as hepco flour.

Hepco Grits.—A granulated "breakfast food" made from and having approximately the same composition as hepco flour.

To prepare hepco flour, soy beans are cleaned and cooked with a little salt, then dried and ground. The flour is sifted and reground. Hepco dodgers are made according to the following recipe: 1¼ pounds of hepco flour; ½ teaspoonful of salt; mix well and add ¾ cupful of milk and 1 cupful of cold water; 2 eggs which have been thoroughly beaten. Beat the whole mixture together into a cooky batter, roll out to ¼ inch thickness, cut with a cooky cutter and bake on well-buttered tins in hot oven. This recipe will make about three dozen dodgers. The dodgers are made up for shipping purposes by having a pure gelatine mixed in with the flour and then rolled out.

Hepco grits are made according to the recipe for hepco dodgers. The material is thoroughly dried out and put through a bread crumber.

HOYT'S GLUTEN SPECIAL FLOUR.—A gluten flour containing protein, 80 per cent, fat, 1 per cent, and starch, less than 5 per cent.

Actions and Uses.—Hoyt's gluten special flour may be given when a diet relatively free from carbohydrate is desired, especially in diabetes. It is claimed to make satisfactory bread, and may be used to prepare muffins, flat cakes or gruel.

The nutritive value of 500 Gm. of Hoyt's gluten special flour corresponds approximately to 1,810 calories, of which 1,640 are yielded by protein, 45 by fat, and 125 by carbohydrate.

Manufactured by the Pure Gluten Food Company, New York. No U. S. patent or trademark.

Hoyt's gluten special flour is prepared by washing a wheat flour dough with cold water until the gluten content of the wheat has been as completely freed from starch as is possible by mechanical means. The residual mass is then dried and ground.

LISTER'S CASEIN-PALMNUT DIETETIC FLOUR.—Casein 52 per cent, sodium caseinate 22 per cent, palmnut 18 per cent, to which has been added a leavening mixture consisting of sodium bicarbonate, 4 per cent, and acid calcium phosphate, 4 per cent.

Actions and Uses.—This flour is employed in conditions in which carbohydrate is contraindicated, such as diabetes.

The nutritive value of 500 Gm. of Lister's prepared casein dietetic flour corresponds approximately to 1,170 calories, of which 1,147 are yielded by protein and 23 by fat.

Dosage.—Lister's casein-palmnut dietetic flour is adapted for the preparation of muffins, biscuits, cookies, cakes, etc.

Manufactured by Lister Bros., Inc., New York. No U. S. patent or trademark.

MAC DOWELL'S WHEAT-NUT-CASEIN DIETETIC FLOUR.—A flour prepared from wheat, edible nuts and casein, to which has been added a leavening mixture composed of potassium bitartrate and sodium bicarbonate and sodium chloride as flavoring. The product has approximately the following composition: protein, 28.67; carbohydrate, 28.68; fat, 18.69; ash, 5.64; fiber and pentosans, 7.59; and water, 8.49.

Actions and Uses.—MacDowell's wheat-nut-casein dietetic flour is proposed for use in the dietetic treatment of diabetes and wherever restriction of carbohydrate in the diet is desired. The nutritive value of 500 Gm. of MacDowell's wheat-nut-casein dietetic flour corresponds approximately to 2,190 calories, of which 588 are yielded by protein, 696 by carbohydrate, and 906 by fat.

Manufactured by MacDowell Brothers, Ogdensburg, N. Y. No U. S. patent. U. S. trademark 202,030.

SOY BEAN GRUEL FLOUR.—A flour prepared from the soy bean, having approximately the following composition: protein, 44; fat, 20; sucrose, 10; ash, 4.3; fiber, 2, and water, 4.6.

Actions and Uses.—Soy bean gruel flour may be used for preparing muffins. It is indicated in cases in which a diet relatively free from carbohydrate is desired, as in diabetes and amylaceous dyspepsia. It has also been suggested for use in the diet in obesity. The nutritive value of 500 Gm. of this flour corresponds approximately to 2,027 calories, of which 902 are yielded by protein, 205 by carbohydrate, and 920 by fat.

Manufactured by Cereo Company, Tappan, N. Y. No U. S. patent or trademark.

Soy bean gruel flour is made from soy bean with the removal of as much of the hull as is practicable.

SOBEE.—A mixture of soy bean flour 67.5 per cent and barley flour 9.5 per cent, to which has been added olive oil 19.0 per cent, sodium chloride 1.3 per cent, and calcium carbonate 2.7 per cent. The approximate analysis of powdered sobee is: fat 22.50, protein 33.20, carbohydrate (barley and soy bean starches) 32.61, ash 8.51, moisture 3.18. The nutritive value of 500 Gm. is approximately equivalent to 2,223 calories.

Action and Uses.—Sobee is used as a substitute in the diet of infants who are sensitive to the proteins of milk.

Dosage.—The normal dilution of sobee is used according to the age and weight of the child. The normal dilution is prepared by adding 1 ounce by weight (6 level tablespoonfuls) of sobee to 7 ounces of water and bringing to boiling temperature. This dilution represents approximately fat 2.81, protein 4.15, carbohydrate 4.07, salts 1.06. The p_H of this mixture is 7.2 and the nutritive value of 1 fluidounce is approximately equivalent to 17 calories. This is the average feeding, to which may be added 15 Gm. (1 level tablespoonful) of a suitable carbohydrate.

Manufactured by Mead Johnson & Co., Evansville, Ind. No U. S. patent. U. S. trademark 252,447.

Sobee is prepared by mixing soy bean flour 67.5 parts and barley flour 9.5 parts with a suitable amount of water and cooking; after cooking, olive oil 19.0 parts, sodium chloride 1.3 parts, and calcium carbonate 2.7 parts are added; the mixture is homogenized, dried and then packed in hermetically sealed cans in an atmosphere of nitrogen. Its composition is determined by the usual methods of the American Association of Agricultural Chemists except for the fat, which is determined as follows: Approximately 1 Gm. of powdered sobee weighed accurately is placed in a flask; 9 to 10 cc. of water, 1 to 1.5 cc. of stronger ammonia water and 10 cc. of alcohol are added; the flask is shaken; 25 cc. each of ethyl ether and petroleum ether are added; the flask is then shaken and centrifugated at moderate speed for thirty seconds; the combined ether solution is poured off into a tared aluminum dish; the extraction with 10 cc. of alcohol and 25 cc. each of ethyl ether and petroleum ether is repeated and the combined ether solution again poured off into the same aluminum dish; the solvents are evaporated and the remainder dried to constant weight: the increase in weight represents the fat content of sobee.

Carbohydrate Foods

Prepared carbohydrate foods are used for the nutrition of infants and for the purpose of modifying bacterial action in the intestinal tract. The majority of the carbohydrate foods are prepared from starch by the action of amylolytic enzymes, heat or acids, and are mixtures of dextrin, maltose or glucose (dextrose). Glucose of high purity may be administered intravenously or subcutaneously. The other sugars are not suitable for parenteral administration. Lactose, or sugar of milk, is used in dietetics chiefly for the purpose of promoting the development of aciduric organisms in the alimentary tract. The calorific value of the carbohydrate foods is determined on the assumption that 1 Gm. of dry carbohydrate is equivalent to 4.1 calories.

BORCHERDT'S MALT SUGAR.—A mixture containing approximately: maltose 87.40 per cent; dextrin 4.35 per cent: protein 4.40 per cent; ash 1.90 per cent, and moisture 1.95 per cent.

Actions and Uses.—Borcherdt's malt sugar may be used where maltose is indicated in the feeding of infants, particularly in the treatment of constipation. The nutritive value of 500 Gm. of Borcherdt's malt sugar corresponds to approximately 1,985 calories.

Dosage.—It may be used in all milk mixtures in the same proportions as lactose (sugar of milk), that is, 1 ounce (30 cc.) of Borcherdt's malt sugar (2 tablespoonfuls) to a 20 ounce mixture.

Manufactured by Borcherdt Malt Extract Co., Chicago. No U. S. patent. U. S. trademark 64,467.

Borcherdt's malt sugar is prepared by the action of malt diastase on starch.

It is a pale brownish-yellow powder having a malt odor and a sweet taste. It is somewhat hygroscopic and soluble in water.

If a few drops of iodine solution are added to an aqueous solution of Borcherdt's malt sugar (1 in 10) no reddish-violet or blue color is produced.

The maltose content of Borcherdt's malt sugar is determined according to the method described in Bulletin 107, p. 46, U. S. Dept. of Agriculture, Bureau of Chemistry.

The protein content of Borcherdt's malt sugar is calculated from the nitrogen content (N × 6.25) as determined by the method described in Bulletin 107, p. 5, U. S. Dept. of Agriculture, Bureau of Chemistry.

DEXTRI-MALTOSE NO. 1, MEAD'S.—A mixture containing: maltose 51.0 per cent; dextrin 42.0 per cent; sodium chloride 2.0 per cent, and moisture 5.0 per cent.

Actions and Uses.—On the claim that maltose is more readily assimilated than other forms of sugar, Mead's dextri-maltose no. 1, is proposed to supplement the carbohydrate of cow's milk. The nutritive value of 500 Gm. of dextri-maltose corresponds to approximately 1,920 calories.

Dosage.—Mead's dextri-maltose no. 1 may be used in amounts to meet the carbohydrate requirements of infants in place of other carbohydrates.

Manufactured by Mead Johnson & Company, Evansville, Ind. No U. S. patent. U. S. trademarks 136,483 and 154,589.

DEXTRI-MALTOSE NO. 2, MEAD'S.—A mixture containing: maltose, 52.0 per cent; dextrin, 43.0 per cent, and moisture, 5.0 per cent.

Actions and Uses.—On the claim that maltose is more readily assimilable than other forms of sugar, Mead's dextri-maltose no. 2 is proposed for use in the diet of adult invalids. The nutritive value of 500 Gm. of Mead's dextri-maltose no. 2 corresponds to approximately 1,960 calories.

Dosage.—Mead's dextri-maltose no. 2 may be used in amounts to meet the carbohydrate requirements of the invalid in place of other carbohydrates.

Manufactured by Mead Johnson & Company, Evansville, Ind No U. S. patent. U. S. trademarks 136,484 and 154,589.

DEXTRI-MALTOSE NO. 3, MEAD'S.—A mixture containing: maltose, 51.0 per cent; dextrin, 41.0 per cent; potassium bicarbonate, 3.0 per cent, and moisture, 5.0 per cent.

Actions and Uses.—On the claim that maltose is more readily assimilable than other forms of sugar, Mead's dextri-maltose no. 3 is proposed to supplement the carbohydrate of cow's milk. In the belief that an addition of potassium salts counteracts a tendency to constipation, it is said to be particularly adapted for the feeding of constipated infants. The nutritive value of 500 Gm. of Mead's dextri-maltose no. 3 corresponds to approximately 1,920 calories.

Dosage.—Mead's dextri-maltose no. 3 may be used in amounts to meet the carbohydrate requirements of infants in place of other carbohydrates.

Manufactured by Mead Johnson & Company, Evansville, Ind. No U. S. patent. U. S. trademarks 128,783, 136,485 and 154,589.

Mead's dextri-maltose is prepared by the action of diastase on starch. It is a pale yellowish-white, granular, odorless powder, having a faintly sweetish taste. It is somewhat deliquescent on exposure to the air. It is soluble in water.

If a few drops of iodine solution are added to an aqueous solution of Mead's dextri-maltose (1 in 10) a reddish violet but not a blue color is produced.

The maltose in Mead's dextri-maltose is determined by the Fehling volumetric method as described in Leach's "Food Inspection and Analysis," ed. 2, p. 591, but instead of the factor there given the Fehling's solution is standardized against a 0.5 per cent solution of maltose.

HORLICK'S MALTOSE-DEXTRIN MILK MODIFIER.—A mixture containing approximately: maltose, 63 per cent; dextrin, 19.5 per cent; protein, 11.5 per cent; fat, 1.4 per cent; moisture, 2 per cent, and ash, 2.6 per cent.

Actions and Uses.—On the claim that maltose is more readily assimilable than other forms of sugar, Horlick's maltose-dextrin milk modifier is proposed to supplement the carbohydrate of cow's milk.

Dosage.—Horlick's maltose-dextrin milk modifier may be used in amounts to meet the requirements of a desired feeding schedule.

Manufactured by Horlick's Malted Milk Corporation, Racine, Wis. No U. S. patent or trademark.

Horlick's maltose-dextrin milk modifier is prepared by the action of diastase on wheat flour in the presence of water. The extraction is brought to dryness under a high vacuum. Approximately 2 per cent of potassium bicarbonate is added in the manufacture of the product; about 0.66 per cent while the product is in the liquid extractive state, and about 1.34 per cent after the product has been dried.

Horlick's maltose-dextrin milk modifier is an ivory colored or cream white powder, having a sweet taste. It is soluble in water or milk and is slightly hygroscopic. When in an aqueous solution (1 in 20) it is neutral or slightly alkaline to phenolphthalein and is alkaline to methyl orange.

Add a few drops of solution of iodine to an aqueous solution of Horlick's maltose-dextrin milk modifier (1 in 10): no blue color is produced (*absence of starch*).

Determine the maltose content of Horlick's maltose-dextrin milk modifier gravimetrically by the Munson & Walker method. Determine the fat content by extraction in an extraction tube, using the neutral Roese-Gottleib method; evaporate the extraction and weigh the residue. Determine the protein content by calculation from the nitrogen content as found by the Kjeldahl-Gunning-Arnold method.

DEXTROSE.—For description, see the U. S. Pharmacopeia under **Dextrosum.**

Ampoules Dextrose 50 Per Cent, 20 Cc.: Each ampule contains 20 cc. of a 50 per cent solution of dextrose-U. S. P.

Prepared by Swan-Myers Company, Indianapolis.

Ampoules Dextrose 50%, 50 cc.—Each ampule contains 50 cc. of a 50 per cent solution of dextrose, U. S. P.

Prepared by Swan-Myers Company, Indianapolis.

Ampules Dextrose, U. S. P., 10 Gm., 20 cc.: Each ampule contains dextrose, U. S. P., 10 Gm., in distilled water to make 20 cc.; buffered with sodium glycerophosphate, 0.03 per cent.

Prepared by the Abbott Laboratories, North Chicago.

Ampules Dextrose, U. S. P., 25 Gm., 50 cc.: Each ampule contains dextrose, U. S. P., 25 Gm., in distilled water, 50 cc.; buffered with sodium glycerophosphate, 0.03 per cent.

Prepared by the Abbott Laboratories, North Chicago.

Ampoules Glucose (dextrose, U. S. P.) Lilly 10 Gm., 20 cc.: Each ampule contains dextrose, U. S. P., 10 Gm.; cresol, 0.1 per cent.; distilled water, to make 20 cc.; buffered with sodium phosphate.

Prepared by Eli Lilly & Co., Indianapolis.

Ampoules Glucose (dextrose, U. S. P.) Lilly 25 Gm., 50 cc.: Each ampule contains dextrose, U. S. P., 25 Gm.; distilled water to make 50 cc.; accompanied by an ampule containing 2 cc. of a buffer solution which contains in 100 cc. sodium chloride, 0.9 Gm., and sufficient sodium phosphate (approximately 4.5 Gm.) to bring the resulting combination of buffer and glucose solution to a hydrogen ion concentration of p_H 7.

Prepared by Eli Lilly & Co., Indianapolis, Ind.

Glaseptic Ampoules Solution Glucose, 50 per cent, 20 cc.: Each ampule contains dextrose, U. S. P., 10 Gm., in distilled water, to make 20 cc.; buffered with sodium citrate, 0.25 per cent.

Prepared by Parke, Davis & Co., Detroit.

Glaseptic Ampoules Solution Glucose, 50 per cent, 50 cc.: Each ampule contains dextrose, U. S. P., 25 Gm., in distilled water, to make 50 cc.; buffered with sodium citrate, 0.25 per cent.

Prepared by Parke, Davis & Co., Detroit.

EXTRACT OF MALT.—For description see the U. S. Pharmacopeia under Extractum Malti.

Actions and Uses.—Malt extract is useful as a vehicle in pharmacy and as an adjunct in the dietary of infants. Malt extract possesses a distinct laxative effect, due largely to the extractives contained, and it is for this laxative effect that it finds its chief use in infant feeding. The nutritive value of 500 Gm. of malt extract varies from about 1,400 calories to about 1,600 calories, of which approximately from 60 to 80 calories are due to protein. The same quantity of milk represents 360 calories of which 72 are due to protein and 98.4 to carbohydrate.

Dosage.—One-half fluidounce (15 cc.); children's dosage in proportion to age.

Borcherdt's Malt Extract (Plain).—A preparation essentially similar to extract of malt, U. S. P., but containing 10 per cent of glycerin.

Actions and Uses.—See preceding article, Extract of Malt.

Manufactured by Borcherdt Malt Extract Co., Chicago. No U. S. patent. U. S. trademarks 64,467 and 64,441.

Borcherdt's Malt Cod Liver Oil and Iron Iodide (See under Cod Liver Oil).

Borcherdt's Malt Extract with Cascara Sagrada (See under Cascara Sagrada).

Borcherdt's Malt Extract with Cod Liver Oil (See under Cod Liver Oil).

Borcherdt's Malt Extract with Creosote (See under Creosote).

Borcherdt's Malt Soup Extract: a mixture obtained by adding potassium carbonate 1.1 Gm. to each hundred grams of malt extract, according to the formula of Dr. Keller, Universitäts-Kinderklinik, Breslau, Germany.

Loeflund's Malt Extract.—A preparation essentially similar to extract of malt, U. S. P.

Actions and Uses.—See preceding article, Extract of Malt.

Manufactured by Ed. Loeflund & Co., G. m. b. H., Grunbach-Stuttgart (Germany) (Britt, Loeffler & Weil, New York distributor). No U. S. patent or trademark.

Malt Extract (Unmedicated)-P. D. & Co.—A preparation essentially similar to extract of malt, U. S. P., but containing 10 per cent of glycerin. One Gm. of Malt Extract (Unmedicated)-P. D. & Co. converts 5 to 7 Gm. of starch to maltose and dextrin in thirty minutes at 40 C. by the assay method of the U. S. Pharmacopeia for Diastase.

Actions and Uses.—See preceding article, Extract of Malt.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

Malt Extract with Cod Liver Oil-P. D. & Co. (See under Cod Liver Oil).

Maltine.—A preparation essentially equivalent to extract of malt, U. S. P., but containing 3.88 per cent of alcohol. Maltine is prepared from malted barley, oats, and wheat. As determined by a modification of the method of Chick and Roscoe (Biochem. J., XXI, p. 689, 1927), maltine contains one unit per Gm. (28 units per oz.) of vitamin B_1, one unit being the weight of the product necessary as the sole source of B_1 in an otherwise adequate diet to protect growing rats from polyneuritis and to assure normal growth; and ⅓ unit per Gm. (9 units per oz.) of vitamin B_2, one unit being the weight of the product necessary as the sole source of B_2 in an otherwise adequate diet to protect growing rats from pellagra and to assure normal growth. One gram of maltine converts 5 to 7 Gm. of starch to maltose and dextrin in thirty minutes at from 40 to 42 C.

Actions and Uses.—See preceding article, Extract of Malt.

Manufactured by The Maltine Company, Brooklyn. No U. S. patent. U. S. trademark 44,566.

Maltine with Cascara Sagrada (See under Cascara Sagrada).
Maltine with Cod Liver Oil (See under Cod Liver Oil).
Maltine with Creosote (See under Creosote).
Maltine Ferrated (See under Soluble Iron Pyrophosphate).
Malto-Yerbine (See under Eriodictyon).

BORCHERDT'S DRI-MALT SOUP EXTRACT.—A mixture obtained by adding potassium carbonate 1.1 Gm. to each one hundred grams of malt extract, diluted with one-half its volume of distilled water, evaporating the mixture *in vacuo* and drying the residue to a powder by a special drying process. Each one hundred grams contains: maltose, 71.1 Gm.; dextrin, 13.5 Gm.; protein, 8.7 Gm.; salts, 2.9 Gm., and moisture, 3.8 Gm. The nutritive value of 500 Gm. of Borcherdt's dri-malt soup extract corresponds approximately to 1,812 calories, of which 1,734 calories are yielded by carbohydrate.

Actions and Uses. — Borcherdt's dri-malt soup extract is intended for use in preparing a malt soup somewhat similar to that proposed by Dr. Keller, Universitäts-Kinderklinik, Breslau, Germany.

Dosage.—To prepare Keller's malt soup, dissolve 3 ounces by weight (or 5 rounded tablespoonfuls) of Borcherdt's dri-malt soup extract in 22 fluidounces of warm water. Mix 1⅝ ounces by weight (or 3 rounded tablespoonfuls) of wheat flour in 11 fluidounces of milk, strain through a sieve or cloth. Mix the malt soup extract solution and the flour-milk mixture and heat in a double boiler, stirring repeatedly, for five minutes.

Manufactured by Borcherdt Malt Extract Co., Chicago. U. S. trademark 64,467.

BORCHERDT'S DRI-MALT SOUP EXTRACT WITH WHEAT FLOUR.—A powder obtained by evaporating to dryness by a special process a mixture of 100 Gm. of malt soup extract and 50 Gm. of wheat flour, previously made into a paste by boiling with water.

Actions and Uses.—Borcherdt's dri-malt soup extract with wheat flour is designed for use in preparing a malt soup somewhat similar to that proposed by Dr. Keller, Universitäts-Kinderklinik, Breslau, Germany.

Dosage.—To prepare malt soup with wheat flour: Dissolve 4½ ounces by weight (or 7½ rounded tablespoonfuls) of Borcherdt's dri-malt soup extract with wheat flour in 22 fluidounces of warm water (previously boiled), add this to 11 fluidounces of milk.

Manufactured by Borcherdt Malt Extract Co., Chicago. U. S. trademark 64,467.

LOEFLUND'S MALT SOUP STOCK (DR. KELLER'S FORMULA).—A preparation essentially similar to extract of malt, U. S. P., but containing a small amount of potassium carbonate. It contains in 100 Gm.; maltose, 54.26 Gm.; dextrin, 17.60 Gm.; protein, 3.73 Gm.; inorganic salts, 2.11 Gm., and water, 22.30 Gm.

Actions and Uses.—Loeflund's malt soup stock is designed for use in preparing the malt soup of Dr. Keller Universitäts-Kinderklinik, Breslau, Germany. The nutritive value of 500 Gm. corresponds approximately to 1,550 calories.

Dosage.—To prepare malt soup: 50 Gm. (1½ ounces) of wheat flour are beaten with ⅓ liter (about 10 fluid ounces) of cow's milk and the mixture passed through a sieve: 100 Gm. (3 ounces) of Loeflund's malt soup stock are dissolved in ⅝ liter (about 20 fluid ounces) of water at a temperature of 50 C. and the solution heated nearly to the boiling point. To this is then added the milk and flour mixture, and the whole is heated with constant stirring for from 3 to 5 minutes longer. The cooked product is placed in sterilized bottles.

Britt, Loeffler & Weil, New York, distributor. No U. S. patent or trademark.

Loeflund's malt soup stock is a dark brown, syrupy liquid, having a faint, malt-like odor and a sweet taste. Soluble in water; also soluble in milk.

MEAD'S DRY MALT SOUP STOCK.—A mixture containing in 100 Gm.: maltose, 23.5 per cent; dextrin, 23.5 per cent; wheat flour, 46.5 per cent; potassium bicarbonate, 1.5 per cent, and moisture, 5 per cent.

Actions and Uses.—Mead's dry malt soup stock is designed for use in preparing a malt soup somewhat similar to that proposed by Dr. Keller, Universitäts-Kinderklinik, Breslau, Germany.

Dosage.—To prepare malt soup: Mix prescribed amounts of Mead's dry malt stock with sufficient milk to make a thin paste. Add the remainder of the prescribed quantity of milk and water. Boil for fifteen minutes, stirring constantly to avoid burning. Do not use a double boiler. For babies under 3 months of age: Take 1 part of whole milk (from 7 to 10 ounces); 2 parts of water (from 14 to 20 ounces); 2 rounded tablespoonfuls of Mead's dry malt soup stock. Feed 2 or 3 ounces every two hours; ten feedings in twenty-four hours. For babies over 3 months of age: Take 1 part whole milk—1 part of water (from 12 to 24 ounces of each); from 2 to 4 rounded tablespoonfuls of Mead's dry malt soup stock. Feed from 4 to 8 ounces (in accordance with age and weight) every two and one half to three hours, from six to eight feedings in twenty-four hours.

Manufactured by Mead Johnson & Company, Evansville, Ind. U. S. patent 1,171,724 (Feb. 15, 1916; expires 1933).

LACTO-DEXTRIN.—A mixture composed of lactose, 73 per cent; dextrin, 25 per cent; and desiccated lemon juice, 2 per cent.

Actions and Uses.—The administration of lacto-dextrin is proposed as a means of promoting the growth of the normally present aciduric organisms *B. acidophilus* and *B. bifidus* in the alimentary tract so as to make them the predominating organisms. It is claimed that this increased growth of acidophile organisms prevents the undue development of putrefactive bacteria and their products. It is claimed that this change in the character of the intestinal flora brings about increased intestinal activity and that this in turn prevents or ameliorates certain conditions commonly ascribed to putrefactive products in the colon.

Dosage.—From 50 to 120 Gm. (2 to 4 ounces) dissolved in four times its bulk of hot water, three times a day preferably half an hour or an hour before meals. The nutritive value of 500 Gm. of lacto-dextrin corresponds approximately to 1,900 calories.

Manufactured by the Battle Creek Food Company, Battle Creek, Mich. No U. S. patent. U. S. trademark 178,414.

SQUIBB'S VITAVOSE.—A maltose-dextrin preparation representing the water-soluble extractives of malted wheat germ. It is composed, approximately, of maltose, 38 per cent;

malto-dextrins, 20 per cent; dextrins, 20 per cent; soluble proteins, 8 per cent; soluble amino and other nitrogenous substances, 7 per cent; mineral salts, 4 per cent (iron in the form of natural iron salts, 0.0125 per cent); moisture, 3 per cent. It is standardized physiologically to contain at least 100 times the amount of vitamin B_1 and 33 times the amount of vitamin B_2 contained in fresh, raw, certified, whole cow's milk. The nutritive value of 500 Gm. corresponds to approximately 1,940 calories.

Actions and Uses.—Vitavose is used as an adjunct in the diet of children and invalids and where there is a need for greater amounts of vitamin B than are furnished by the individual's customary diet. It may be used to supplement the carbohydrate and vitamin B content of cow's milk.

Dosage.—Vitavose may be used in milk mixtures in approximately the same proportions by weight as lactose, or in amounts to meet the carbohydrate requirements of the invalid in place of or in addition to other carbohydrates. When vitavose is used because of its vitamin B content, the manufacturer recommends that children and adults be given 15 Gm. (1 tablespoonful) one to three times a day.

Manufactured by E. R. Squibb & Sons, New York. U. S. patent 1,541,263 (June 9, 1925; expires, 1942). U. S. trademark 177,061.

Vitavose is prepared by freeing wheat germs of oil, cooking, malting and extracting under conditions designed to assure maximum extraction of the nutritive elements and to preserve the vitamin B content. The clarified extract is then brought to dryness.

It occurs as fine golden-yellow granules possessing an agreeable malty taste. It is very hygroscopic and readily soluble in water.

The maltose in Squibb's vitavose is determined by the Munson and Walker General Method, Official and Tentative Methods of Analysis of the A. O. A. C., ed. 2, p. 190. The dextrin is determined by the method described in Leach: "Food Inspection," ed. 4, p. 654. The estimation of protein, soluble amino and other nitrogenous substances is made by the method described in the "Method of Analysis, A. O. A. C.," 1919, p. 168, chapter 14, par. 5; of moisture, ibid, p. 177, par. 2; of ash (Fe and Ca), ibid, pp. 39-41. Malto-Dextrins are determined by evaporating the alcoholic filtrate and washings to dryness under vacuum and determining the reducing sugars on the residue both before and after inversion, the difference between these results being calculated as dextrose and reported as malto-dextrins (Inversion Method, p. 186, Munson and Walker General Method, p. 190, A. O. A. C., ed. 2). The vitamin B content is determined by a modification of the method described by Osborne and Mendel (*J. Biol. Chem.* **54**: 743, 1922). The vitamin B_2 content is determined by a modification of the rat growth method used by Chick and Roscoe (*Biochem. J.* **21**: 698, 1927), and by Macy et al. (*J. Biol. Chem.* **73**: 204, 1927).

THOMPSON'S MALTOSE AND DEXTRIN.—Thompson's Maltose and Dextrin (with 2 per cent added sodium chloride).—A mixture containing maltose, 51 per cent; dextrins, 45 per cent; sodium chloride, 2 per cent; and moisture, 2 per cent.

Actions and Uses.—On the claim that maltose is more readily assimilated than other forms of sugar, Thompson's maltose and dextrin is proposed to supplement the carbohydrate of cow's milk or of water modifications of cow's milk. The nutritive value of 500 Gm. corresponds approximately to 1,933 calories.

Dosage.—Thompson's maltose and dextrin may be used in amounts sufficient to meet the requirements of a desired feeding schedule.

Manufactured by Thompson's Malted Milk Co., Inc., Waukesha, Wis. No U. S. patent or trademark.

Thompson's maltose and dextrin is prepared by utilizing the diastatic action of barley malt on cereal starches. Two per cent of sodium chloride is added in the manufacture of the product. The maltose is determined by the Munson-Walker general method (Official and Tentative Methods of Analysis of the A. O. A. C., ed. 2, p. 190; dextrin is determined by the method given in Leach: Food Inspection and Analysis, ed. 4, p. 654; moisture is determined by the method given in Official and Tentative Methods of Analysis, A. O. A. C., ed. 2, p. 177, par. 2.

Non-Nutritive Foods

Non-nutritive foods are foods of low nutritive value and are used in the treatment of obesity, diabetes and other conditions in which limited amounts of foods, especially of carbohydrate, are indicated. The non-nutritive foods provide bulk. By supplying "roughage" they relieve constipation, which is likely to occur, on restricted diets. Furthermore, the non-nutritive foods made up into the form of bread, biscuits or crackers provide convenient vehicles for the administration of butter or fats when it is desired to include large amounts of these foods in the diet, as in the treatment of diabetes.

CELLU FLOUR.—Cellulose Flour.—Commercially pure cellulose in the form of flour.

Actions and Uses.—Cellu flour is used as a means of filling out reduced diets. It is a nonnutritive food substitute used to give bulk to foods, thus serving to satisfy hunger without furnishing nourishment.

Dosage.—Cellu flour, after admixture with bran, baking powder, eggs, "India gum," or liquid petrolatum in varying proportions may be used for the preparation of imitation bread, muffins, cookies, griddle cakes, pie-crust, etc. These preparations may be seasoned with salt, spices or saccharin.

Manufactured by The Chicago Dietetic Supply House, Chicago. No U. S. patent. U. S. trademark 133,954.

Purified and bleached wood pulp, straw pulp or cotton fiber is further treated to facilitate grinding to flour.

Cellu flour is white to grayish white in color; odorless and tasteless.

HOFFMAN'S NON-NUTRITIVE NUT FLOUR.—A preparation prepared from Tagua palm nuts, composed chiefly of unassimilable carbohydrates (mannans). It contains fat, 0.63 per cent; protein, 4.13 per cent; moisture, fiber and ash, 14.8 per cent; modified celluloses, 80.44 per cent.

Actions and Uses.—Hoffman's non-nutritive nut flour is used as a means of filling out restricted diets. It is a non-nutritive food substance, used to give bulk to food, thus serving to satisfy hunger without furnishing nourishment. Being unassimilated, it adds roughage to the diet.

Dosage.—Hoffman's non-nutritive nut flour, after admixture with eggs, "India Gum" and baking powder, and seasoned, if desired, with salt, flavoring and saccharin, may be used in the preparation of imitation bread, griddle cakes, etc.

Manufactured by the Efficiency Products Co., Somerville, N. J. No U. S. patent or trademark.

Hoffman's non-nutritive nut flour is a white powder, without taste or odor.

Hoffman's non-nutritive nut flour contains approximately: moisture, 9.05 per cent; ash, 1.00 per cent; protein (nitrogen × 6.25), 4.13 per cent; fiber, 4.75 per cent; nitrogen-free extract: starch, none; soluble carbohydrate (as dextrose), 3.44 per cent; other nitrogen-free extract by difference, 77.00 per cent; fat (ether extract), 0.63 per cent. In this analysis "crude fiber" and "nitrogen-free extract" represent materials belonging to the carbohydrates.

NUTRIVOID FLOUR.—A palm nut flour stated to be derived from parts of the seeds of certain *Phytelephantaceae,* of *Phoenix dactylifera,* and of *Phoenix canariensis,* and to be composed chiefly of unassimilable carbohydrates (mannans). It contains fat, 0.92 per cent; protein, 4.31 per cent; nonutilizable carbohydrate, 85.37 per cent.

Actions and Uses.—Nutrivoid flour is used as a means of filling out restricted diets. It is a non-nutritive food substance, used to give bulk to food, thus serving to satisfy hunger without furnishing nourishment. Being unassimilated, it adds roughage to the diet and thus aids peristalsis.

Dosage.—Nutrivoid flour, after admixture with bran and baking powder, eggs, "India gum" or liquid petrolatum in varying proportions, may be used for the preparation of imitation bread, muffins, cookies, griddle cakes, pie-crusts, etc. These preparations may be seasoned with salt, spices or saccharin.

Manufactured by the Nutrivoid Products Company, Inc., New York. No U. S. patent. U. S. trademark 189,254.

Nutrivoid flour is a white powder, having a slight taste and odor.

Nutrivoid flour contains approximately: moisture, 8.23 per cent; ash, 1.17 per cent; protein (nitrogen x 6.25), 4.31 per cent; crude fiber, 7.18 per cent; nitrogen-free extract; starch none, reducing sugars after hydrolysis, 6.00 per cent; other nitrogen-free extract by difference, 72.1 per cent; fat (ether extract), 0.92 per cent. In this analysis "crude fiber" and "nitrogen-free extract" represent materials belonging to the carbohydrates.

Vitamin Foods

The investigations of nutrition that have been initiated since the second decade of the present century have afforded an entirely new outlook upon many disorders, some of which have long been suspected to be of dietary origin. This is due to the scientific demonstration that in addition to the long recognized foodstuffs or proximate principles — the proteins, carbohydrates and fats — which yield the energy requisite for life and activity and which, along with certain inorganic elements, form the structure of the tissues and the fluids of the organism, other factors also are essential for the preservation of bodily wellbeing and physiologic function. They are at present commonly designated as vitamins.

The vitamins, the precise chemical nature of which still remains unknown, apparently cannot be synthesized by the body, hence they must be furnished preformed together with the long recognized nutrients. Deprivation of these vitamins may lead to symptoms of ill health, some of them outspoken in character, that have given rise to the designation "deficiency diseases" which may be as striking in their manifestations as are the direct results of underfeeding (calorie deficiency) or deprivation of essential inorganic elements such as calcium, chlorine, phosphorus, or iodine. A striking illustration of a "deficiency disease" is presented by scurvy. This can be entirely averted or effectively cured by the inclusion of suitable foods in the diet. It has been clearly established by convincing experiments that the prophylactic or remedial agent — the antiscorbutic substance — is not to be identified with any of the hitherto recognized organic foodstuffs or mineral nutrients. The antiscorbutic substance or vitamin is present in many articles used as food, such as green vegetables and fruits, yet entirely lacking in others such as the common cereals. The antiscorbutic vitamin is readily destroyed by heat under certain conditions, notably in an alkaline medium and in the presence of oxygen. Under other conditions of heating, particularly such as prevail in food preservation by canning, this vitamin is more stable.

The foregoing illustration will suffice to indicate the characteristic feature of a vitamin — a substance essential for maintenance of health; not identical with the familiar nutrients; not synthesized in the body, which therefore depends upon an exogenous supply; sometimes more labile than the foodstuffs proper and hence subject to deterioration; and distributed variously among the edible parts or animals and plants. The existence of more than one vitamin has been postulated because of the discoveries of various dietary deficiency disorders or symptoms that are remediable only by inclusion of different substances in the diet giving clear indication of the need of multiple agents specifically adapted to prevent each type of nutritive disaster.

Thus for convenience the designations vitamins A, B, C, D, etc., have arisen. In addition to scurvy, beriberi, rickets, pellagra, xerophthalmia, and other possibly familiar disease conditions have been attributed with considerable experimental certainty to the lack of suitable vitamins; the protective or curative agents are accordingly sometimes spoken of as the antiscorbutic vitamin, the antirachitic vitamin, the antineuritic vitamin, the antiophthalmic vitamin, etc. Detailed accounts of the physiology of the vitamins can now be found in the newest textbooks on physiologic chemistry and nutrition. The problems raised thereby are the subject of active discussion and extensive investigation so that with respect to many features only tentative conclusions should be announced at this time.

Ordinarily there is no reason why a properly selected diet should not afford an adequate supply of the requisite vitamins. Furthermore, there is no evidence of any noteworthy prevalence in this country of conditions that might properly be ascribed to a lack of one or more vitamins. However, it must be admitted that under circumstances bringing about a highly restricted dietary regimen and leading to "one-sided" diets a relative shortage of some of the vitamins does at times arise. In almost all such instances the situation can be properly corrected by prescription of appropriate foods. Occasionally a corrective result may be more effectively secured by the administration of products especially rich in the desired vitamin; for example, cod liver oil as a dietary adjunct in the prevention or treatment of rickets, and yeast preparations in the relief of pellagra.

The clear indications for such specific vitamin therapy are still few in number. The chief justification for the recognition of special vitamin-bearing products at present applies to unusual concentrations of the desired potent principle that they may represent or to exceptionally desirable dosage forms. These considerations, which may be modified by the progress of research, have served as criteria in the selection of products offered for inclusion in N. N. R. as products rich in specific vitamins at present recognized to have demonstrable value in clinical practice or human nutrition.

MALTINE.—See under Carbohydrate Foods.

SQUIBB'S VITAVOSE.—See under Carbohydrate Foods.

VIOSTEROL IN OIL 100 D.—See under Viosterol.

COD LIVER OIL AND COD LIVER OIL PREPARATIONS

Cod liver oil, in addition to being a fat which is readily digestible and assimilable, has been demonstrated to have by virtue of its vitamin A content definite growth promoting qualities, and by virtue of its vitamin D content a definitely favorable influence in rickets. The Pharmacopeia, besides tests for purity, gives a test for vitamin A potency of cod liver oil. It does not make this obligatory, but stipulates that a product claimed to be assayed must have a potency of at least 50 units per Gm. when tested by the pharmacopeial method. Evidence has accumulated to show that it is feasible to market cod liver oil having a vitamin A potency much higher than the lower limit of the pharmacopeial product, and all brands included in New and Nonofficial Remedies are required to have a vitamin A (antiophthalmic) potency of at least 400 units per Gm. when tested by the pharmacopeial method.

It has been shown that an effective concentrate of cod liver oil can be made and marketed, and one such concentrate has been included in New and Nonofficial Remedies. To be acceptable, such a concentrate should have a vitamin A potency of at least 10,000 U. S. P. units per Gm. (200 U. S. P. units per tablet or other dosage unit).

The methods for determination of vitamin D (antirachitic) potency have not been sufficiently developed to justify the Council in adopting a specified procedure; however, the Council encourages manufacturers to adopt and publish such methods as will enable them to indicate that their products have been demonstrated to be antirachitically potent.

COD LIVER OIL.—Oleum Morrhuae.—For description see the U. S. Pharmacopeia and Useful Drugs.

Borcherdt's Malt Cod Liver Oil and Iron Iodide: Each 100 cc. contains ferrous iodide 0.88 Gm. (2 grains per fluidounce), cod liver oil, 25 cc. and Borcherdt's malt extract (plain) (which see under Extract of Malt) 75 cc. The cod liver oil used is assayed by the method of the U. S. Pharmacopeia to contain approximately 500 vitamin A units per Gm., and is assayed by the method of Poulsson and Loevenskiold (J. Biol. Chem., XXII, no. 1, p. 135, 1928) to have a vitamin D potency such that 0.004 Gm. daily will protect rats from rickets.

Prepared by the Borcherdt Malt Extract Co., Chicago. No U. S. patent. U. S. trademarks 64,467 and 64,441.

Borcherdt's Malt Extract with Cod Liver Oil: Each 100 cc. contains cod liver oil, 25 cc., and Borcherdt's malt extract (plain) (which see under Extract of Malt) 75 cc. The cod liver oil used is assayed by the method of the U. S. Pharmacopeia to contain approximately 500 vitamin A units per Gm., and i sassayed by the method of Poulsson and Loevenskiold (J. Biol. Chem., XXII, no. 1, p. 135, 1928) to have a vitamin D potency such that 0.004 Gm. daily will protect rats from rickets.

Prepared by the Borcherdt Malt Extract Co., Chicago. No U. S. patent. U. S. trademarks 64,467 and 64,441.

Maltine with Cod Liver Oil: Maltine (which see under Extract of Malt) 70 per cent and cod liver oil 30 per cent. Each 100 cc. contains not less than 28,000 fat-soluble vitamin A units as determined by the U. S. Pharmacopeia assay, and the product has an antirachitic potency such that 20 mg. fed daily to rachitic rats is sufficient to cause perceptible to distinct healing of rickets in from 6 to 10 days as determined by the line test.

Prepared by The Maltine Co., Brooklyn. No U. S. patent. U. S. trademark 44,566.

Cod Liver Oil-Squibb.—It has a content of fat soluble vitamin A which is not less than 500 units per Gm., and its antirachitic potency is demonstrated by determining its power of producing a line of recalcification in the leg bones of rachitic rats.

Dosage.—The average adult daily dose is 15 cc. (4 fluidrachms); for children, half this amount or less; for infants, 0.5 to 2.0 cc. (8 to 30 minims) according to age.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

Squibb's Mint-Flavored Cod-Liver Oil: Cod liver oil-Squibb, containing 0.67 per cent of oil of spearmint as flavoring.

Cod liver oil-Squibb complies with the U. S. P. standard for cod liver oil. In addition it is required to have a content of fat soluble (antiophthalmic) vitamin A, determined by the method of the U. S. P., of not less than 500 units per Gm. Its antirachitic (vitamin D) potency is tested by determining the minimum quantity that will give in ten days a continuous line of recalcification, through the rachitic metaphyses of the leg bones of rats fed Steenbock's rickets-producing diet 2965 (J. Biol. Chem. **64**: 263, 1925). Litter mate controls must show completely recalcified metaphyses of the leg bones.

Mead's Standardized Cod Liver Oil.—It has an antirachitic potency such that one-fourth of one per cent cures experimental rickets in rats in five days when added to the diet. It is also required to have a vitamin potency such that 0.002 Gm. will cure ophthalmia in rats.

Manufactured by **Mead Johnson and Co., Evansville, Ind.** No U. S. patent or trademark.

Mead's Standardized Cod Liver Oil, Flavored: Mead's standardized cod liver oil, containing 0.12 per cent of a mixture of vanillin and oil of lavender as flavoring.

Mead's cod liver oil complies with the U. S. P. standards for cod liver oil. In addition it is required to have an antirachitic potency such that one-fourth of one per cent when added to the diet of rats suffering from experimental rickets will cause complete healing of the lesion in five days as determined by the method of McCollum, Simmonds, Shipley and Park (*Proc. Soc. Exp. Biology and Medicine* **19**: 123, 1921). It is also required to have a vitamin potency such that 0.002 Gm. will cure ophthalmias in rats as determined by the method of Zilva and Miura (*Biochem. Jour.* **15**: 654, 1921).

Nason's Palatable Cod Liver Oil.—Cod liver oil containing 0.62 per cent of essential oils as flavoring, having a vitamin A potency such that 0.00125 Gm. per day is adequate to promote the growth of young albino rats and a vitamin D potency such that 0.01 Gm. per day for eight days will cure experimental rickets in rats which have been deprived of vitamin D and of ultraviolet light.

Dosage.—For adults, 2 to 4 cc. (30 to 60 minims) three times a day; for children, 1 to 2 cc. (15 to 30 minims) three times a day.

Manufactured by **Tailby-Nason Co., Boston.** No U. S. patent or trademark.

Nason's palatable cod liver oil complies with the U. S. P. standards for cod liver oil. In addition, it is required to have a content of fat soluble vitamin A, determined by the U. S. P. method, of not less than 800 units per gram, and an antirachitic potency such that 0.01 Gm. per day will produce definite healing (as determined by x-ray photographs), in the leg bones of rachitic rats in eight days when added to a diet lacking in vitamin D, the rats being also deprived of ultraviolet light.

Parke, Davis & Company's Standardized Cod Liver Oil.—It has a content of fat soluble vitamin A which is not less than 500 units per Gm., and a vitamin D potency of not less than 112 units per Gm.

Dosage.—Infants, from 1 to 2 cc. (15 to 30 minims); older children, from 2 to 4 cc. (30 to 60 minims); adults, 4 cc. (1 fluidrachm) or more, three times a day.

Manufactured by Parke, Davis & Co., Detroit. No. U. S. patent or trademark.

Malt Extract with Cod Liver Oil-P. D. & Co.: Each 100 cc. contains Standardized Cod Liver Oil-P. D. & Co., 25 cc. and malt extract (unmedicated)-P. D. & Co. (which see under Extract of Malt) 75 cc. with chocolate and extract of vanilla as flavoring agents.

Parke, Davis & Company's standardized cod liver oil complies with the standards of the U. S. Pharmacopeia. In addition, it is required to have a content of fat soluble vitamin-A, determined by the method of the U. S. P., equivalent to 500 units per Gm. (one unit being the amount required to correct both the induced xerophthalmia and retarded growth of young albino rats) and an antirachitic potency when determined by the method of McCollum, Simmonds, Shipley and Park (*J. Biol. Chem.* **51**: 41 [March] 1922) of not less than 112 units per Gm. (one unit being the amount of cod liver oil required daily to initiate recalcification in the leg bones of young albino rats).

Patch's Flavored Cod Liver Oil.—Cod liver oil containing less than 0.5 per cent of essential oils as flavoring and having a vitamin A potency of not less than 500 vitamin A units to the gram as defined in the U. S. P. X, and a vitamin D potency of not less than 75 units per Gm.

Dosage.—4 cc. (1 fluidrachm) 3 times a day; children, 2 cc. (30 minims) 3 times a day.

Manufactured by The E. L. Patch Co., Boston. No U. S. patent or trademark.

Patch's flavored cod liver oil complies with the U. S. P. standards for cod liver oil. In addition it is required to have a content of fat-soluble vitamin A of not less than 500 units per Gm. (one unit being the least amount required daily to promote a renewal of growth in albino rats that have ceased to grow and may show symptoms of malnutrition such as xerophthalmia, on diets adequate except for vitamin A) and an antirachitic potency, determined by a modification of the method of McCollum, Shipley, and Park, of not less than 75 units per Gm. (one unit being the least amount of cod liver oil required daily for 8 days to promote recalcification in the tibias of young albino rats suffering from experimental rickets).

COD LIVER OIL WITH VIOSTEROL 5 D.—Viosterol dissolved in cod liver oil, the solution containing not less than 400 vitamin A units per Gm. when tested by the pharmacopeial method and 66.65 rat units of vitamin D per Gm., this antirachitic strength being 5 times that of a potent cod liver oil used as a standard.

Actions and Uses.—See preceding article, Viosterol. Cod liver oil with viosterol 5 D is proposed for use in conditions in which it is desired to supplement the administration of vitamin A with that of vitamin D.

Dosage.—For infants and young children, 2.5 to 3.3 cc. (53 to 67 minims) daily; for adults and in severe cases doses up to 7 cc. (140 minims) or more are given.

Cod liver oil with viosterol 5 D is prepared by addition of irradiated ergosterol to cod liver oil in such proportion that the finished product will contain not less than 400 vitamin A units per Gm. when tested by the pharmacopeial method, and 66.65 rat units of vitamin D per Gm., the rat unit being that amount of vitamin D which, when uniformly distributed into the standard vitamin D deficient diet — ration 2965, *Jour. Biol. Chem.* **64**: 623, 1925—will produce a narrow and continuous line of calcium deposits in the metaphyses of the distal ends of the radii and ulnae of standard rachitic rats.

Abbott's Cod Liver Oil with Viosterol 5 D.—A brand of cod liver oil with viosterol 5 D, N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) by license of the Wisconsin Alumni Research Foundation.

Irradiated ergosterol, prepared by the method described under viosterol in oil 100 D-Abbott, is added to cod liver oil and the finished product is required to have a vitamin A potency of not less than 500 pharmacopeial units and to have the vitamin D potency of cod liver oil with viosterol 5 D, N. N. R.

Squibb's Cod Liver Oil with Viosterol 5 D.—A brand of cod liver oil with viosterol 5 D, N. N. R.

Manufactured by E. R. Squibb & Sons, New York, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) by license of the Wisconsin Alumni Research Foundation.

Irradiated ergosterol, prepared by the method described under viosterol in oil 100 D-Squibb, is added to cod liver oil and the finished product is required to have a vitamin A potency of not less than 500 pharmacopeial units and to have the vitamin D potency of cod liver oil with viosterol 5 D, N. N. R.

Squibb's Cod Liver Oil with Viosterol 5 D, Mint-Flavored.—A brand of cod liver oil with viosterol 5 D, N. N. R., containing 0.67 per cent of oil of spermint as flavoring.

Manufactured by E. R. Squibb & Sons, New York, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) by license of the Wisconsin Alumni Research Foundation.

Irradiated ergosterol, prepared by the method described under viosterol in oil 100 D-Squibb is added to cod liver oil containing 0.67 per cent of oil of spearmint as flavoring and the finished product is required to have a vitamin A potency of not less than 500 pharmacopeial units and to have the vitamin D potency of cod liver oil with viosterol 5 D, N. N. R.

OSCODAL.—Cod liver Oil Concentrate-Metz.—A preparation of the nonsaponifiable fraction of cod liver oil, containing the antiophthalmic and antirachitic fat soluble vitamins. It has 200 times the antiophthalmic (vitamin A) potency of cod liver oil-U. S. P. (containing not less than 50 units per Gm.) when assayed by the method of the U. S. P. for cod liver oil, and its antirachitic (vitamin D) potency is such that 0.0002 Gm. of oscodal (equivalent in potency to 0.02 Gm. of the oil) per day will suffice to initiate recalcification in the leg bones of young albino rats in ten days.

Actions and Uses.—Oscodal possesses properties similar to those of cod liver oil so far as these depend on the fat soluble vitamin content of the latter.

The experiments of Dubin and Funk (*J. Metabol. Research* **4**:467, 1923) seem to show that a cod liver oil extract prepared by the method used for the preparation of oscodal is efficient in controlling rickets and ophthalmia in rats on diets deficient in these vitamins. Louis Fischer (*J. Metabol. Research* **4**:481, 1923) has presented evidence to show that oscodal is as efficient in the treatment of clinical rickets as cod liver oil itself.

Dosage.—For infants or children, from 0.01 to 0.04 Gm. and for adults, from 0.04 to 0.06 Gm., three times a day.

Manufactured by the H. A. Metz Laboratories, Inc., New York. U. S. patent 1,629,074 (May 17, 1927; expires 1944). U. S. trademark 210,246.

Oscodal Tablets: Each coated tablet contains oscodal, 0.02 Gm.

Oscodal is manufactured from physiologically standardized cod liver oil which complies with the standards of the U. S. Pharmacopeia X. In addition, the oil is required to have (1) a content of fat soluble vitamin A at least twice that present in the U. S. P. product (which contains not less than 50 units per Gm.) as determined by the U. S. P. assay, and (2) an antirachitic potency determined by the method of McCollum, Simmonds, Shipley and Parke (*J. Biol. Chem.* **51:** 42 [March] 1922) as modified by Steenbock and Black (*J. Biol. Chem.* **64:** 263 [June] 1925) using ration 2965, such that the administration of 0.02 Gm. of oil per day will suffice to initiate recalcification in the leg bones of young albino rats.

Oscodal is required to have 100 times the potency of the oil from which it is made when tested for its antiophthalmic and antirachitic potency by the methods used to assay the cod liver oil from which it is manufactured. To determine the potency of oscodal tablets, 100 tablets are powdered in a glass mortar; the powder is transferred to a paper thimble, placed in a Soxhlet extractor, and extracted with ether; the ether is evaporated off and the remaining material dissolved in vitamin-free peanut oil in the proportion of 1 to 100; the oil solution is then tested for its vitamin potency.

Modified Milk Products

ALBUMIN MILK-HOOS.—Dry Protein Milk.—A modified milk preparation having a relatively high protein content and a relatively low carbohydrate content. Each 100 Gm. contains, approximately, protein, 38 Gm.; butter fat, 29 Gm.; lactose (milk sugar), 22 Gm.; ash, 5 Gm., and small amounts of free lactic acid.

Actions and Uses.—When suitably mixed with water, albumin milk-Hoos is said to be useful for correcting intestinal disorders of infants and children.

Dosage.—In general, albumin milk-Hoos should be administered in small quantities according to age and condition of the patient, after a period of starvation of from twelve to forty-eight hours. Suitable carbohydrates may gradually be added to the preparation as indicated by the clinical conditions.

To prepare albumin milk for use, the contents of one small package of albumin milk-Hoos (3 ounces) are sprinkled on the surface of 1 quart of warm, previously boiled water, and the mixture is beaten with an egg beater or wire whip. After mixing, the product is poured twice through a fine strainer, the curds being rubbed through with a spoon. Greater dilutions are sometimes prescribed. Carbohydrates, if prescribed, are dissolved in a little warm water and added to the mixture. The finished product contains approximately 3.1 per cent of protein, 2.4 per cent of fat, 1.8 per cent of lactose and 0.4 per cent of ash.

Louis Hoos, Chicago, distributor. No U. S. patent. U. S. trademark 89,033.

MEAD'S POWDERED BOILABLE PROTEIN MILK.—A modified milk preparation having a relatively high protein content and a relatively low carbohydrate content. Each 100 Gm. contains approximately protein, 39 Gm.; butter fat, 27 Gm.; lactose, 24 Gm.; free lactic acid, 2 Gm.; ash, 6 Gm.; and moisture, 2 Gm.

Actions and Uses.—When suitably mixed with water, powdered boilable protein milk is useful for correcting intestinal disorders of infants and children. The nutritive value of 500 Gm. of the dry powder corresponds approximately to 2,535 calories.

Dosage.—For the majority of conditions powdered boilable protein milk should be given in small quantities according to the age and condition of the patient and, in cases of diarrhea, after a period of starvation of from twelve to twenty-four hours. Suitable carbohydrate may be gradually added to the feeding, as indicated by the clinical conditions.

To prepare the normal dilution of powdered boilable protein milk for use, 1 ounce (4 level tablespoonfuls) is placed on the surface of 11 fluidounces of cold, previously boiled, water and then beaten with an egg beater. The mixture may be heated to boiling and, while stirring, boiled for five to ten minutes. Carbohydrates, if prescribed, can be added at the time the powdered boilable protein milk is added to the water. One hundred cc. of the normal dilution, without additional carbohydrate, contains approximately 3.16 Gm. of protein, 2 Gm of lactose, 2.25 Gm. of butter fat, and 0.17 Gm. of free lactic acid. This dilution has a p_H of 5.2. The nutritive value of 500 Gm. corresponds approximately to 230 calories.

Manufactured by Mead Johnson and Company, Evansville, Ind. No U. S. patent or trademark.

MEAD'S POWDERED LACTIC ACID MILK NON-CURDLING, NO. 1, WITH DEXTRI-MALTOSE.—A modified milk product prepared by adding lactic acid, U. S. P., and a maltose-dextrin preparation to whole milk, heating, drying, and powdering. Each 100 Gm. contains, approximately, protein, 18.3 Gm.; lactose, 25.5 Gm.; maltose, 15.17 Gm.; dextrins, 14.38 Gm.; butter fat, 19.15 Gm.; ash, 4.22 Gm.; lactic acid, 1.75 Gm., and moisture, 1.50 Gm.

Actions and Uses.—Mead's powdered lactic acid milk non-curdling, no. 1, with dextri-maltose, is proposed for use in the feeding of infants when it is desired to prescribe an acidulated milk with a certain amount of added carbohydrate.

Dosage.—From 12 to 40 fluidounces of the normal dilution daily, depending on the age, weight and tolerance of the individual infant. To prepare the normal dilution, add to each 1½ fluidounces of water 1 packed level tablespoonful of Mead's powdered lactic acid milk non-curdling, no. 1, with dextri-maltose and stir into solution with an egg-beater. This dilution contains approximately, protein, 3.32 per cent; carbohydrate, 10 per cent; butter fat, 3.48 per cent; ash, 0.78 per cent, and lactic acid, 0.32 per cent. The finished mixture has a p_H of 4.6 and each fluidounce has a nutritive value corresponding to approximately 25 calories.

Manufactured by Mead Johnson & Co., Evansville, Ind. No U. S. patent or trademark.

POWDERED PROTEIN MILK-MERRELL-SOULE.—Dry Protein Milk.—A modified milk preparation having a relatively high protein content and a relatively low carbohydrate content. Each 100 Gm. contains approximately protein, 38 Gm.; butter fat, 27 Gm.; free lactic acid, 3 Gm.; lactose, 24 Gm., and ash, 5 Gm.

Actions and Uses.—When suitably mixed with water, powdered protein milk is said to be useful for correcting intestinal disorders of infants and children. It is claimed that the preparation is especially satisfactory because of the flocculent nature of the casein.

Dosage.—In general, powdered protein milk should be administered in small quantities according to age and condition of the patient, after a period of starvation of from twelve to forty-eight hours. Suitable carbohydrates should be added to the preparation as indicated by the clinical conditions.

To prepare protein milk for use, 1 ounce (3½ tablespoonfuls) of powdered protein milk is placed on the surface of 11 fluidounces of previously boiled water and the mixture stirred with an egg beater or other means of agitation. Greater dilutions are sometimes prescribed. Carbohydrates are dissolved in a little warm water and added to the protein milk, and then sufficient boiled water is added to make 12 fluidounces. One hundred cc. of the finished mixture, without additional carbohydrate, contains approximately 3.4 Gm. of protein, 3.4 Gm. of butter fat, 4.1 Gm. of lactose, and 0.7 Gm. of ash. The finished mixture has a p_H of 4.6.

Manufactured by the Merrell-Soule Company, Inc., 350 Madison Ave., New York City. No U. S. patent or trademark.

PROTEIN S. M. A. (ACIDULATED).—A modified milk preparation having a relatively high protein content and a relatively low carbohydrate content. Each 100 Gm. contains approximately protein (of milk), 35 Gm.; S. M. A. fat (consisting approximately of tallow oil 0 to 10 per cent; coconut oil, 15 per cent; cacao butter, 20 per cent; cod liver oil, from 7.5 to 12.5 per cent; tallow, from 45 to 55 per cent), 20 Gm.; cod liver oil, 2 Gm.; carbohydrate (lactose), 28 Gm.; ash, 6 Gm.; moisture, 2 Gm.; desiccated lemon juice, equivalent to 16.7 cc. of fresh juice. The content of lactic acid is regulated so that when the product is diluted according to directions the liquid will have a p_H of 4.6. The cod liver oil used in this product has a vitamin D potency such that rats fed on Steenbock's diet 2965 are completely protected from rickets by doses of 0.005 Gm. of the oil.

Actions and Uses.—Protein S. M. A. (acidulated) is stated to differ from protein milk in that, when prepared according to directions, it is higher in protein and lower in carbohydrate. Its use in the feeding of infants is proposed as a means of checking diarrhea; in malnutrition and marasmus, and the feeding of prematurely born infants needing a high caloric intake.

Dosage.—For use, one ounce of protein S. M. A. (acidulated) is mixed with 9 fluidounces of warm water; first a smooth paste is made with a little warm water and then the remainder is added with thorough stirring. The mixture is added to the diet in increasing quantities as indicated; carbohydrates may be added.

When diluted according to directions the mixture contains protein, 3.5 per cent; fat, 2.2 per cent; carbohydrate, 2.8 per cent; ash, 0.6 per cent; it has a p_H of 4.6 and represents 50 calories per hundred cc. (15 calories per ounce).

Manufactured by the Laboratory Products Co., Cleveland. No U. S. patent. U. S. trademark applied for.

Foods for Diabetics

In diabetes the essential qualifications of the diet are that there shall be sufficient protein given to meet the minimal protein requirements, an amount of carbohydrate barely in excess of the amount necessary to prevent ketosis and sufficient fat to provide the additional food necessary to meet the caloric requirements. The caloric requirements and the protein requirements are determined chiefly by the age and weight, the carbohydrate requirement by application of the formula of Woodyatt, or of Shaffer. When the minimal amount of carbohydrate cannot be given without the appearance of glycosuria, insulin administration is required. Whether or not glycosuria occurs, any considerable excess of carbohydrate above the minimal requirement should be avoided and inasmuch as more than 50% of the protein of the diet may be converted into sugar, it is also essential that the protein intake be restricted. The total diet should be exactly prescribed in carbohydrate, protein, fat and total calories. The preparation of such a diet is possible with natural foods of known composition. Special food preparations have a place in giving a variety to the diet and when the composition of these is accurately known they are permissible, although rarely necessary. These are usually foods designed to take the place of bread in the diet, and contain a minimum of carbohydrate, but considerable protein. These are described under the Protein Foods. In using such food, due allowance must be made for the conversion of protein into carbohydrate. Diabetics should not be treated by the use of mere lists of permissible and forbidden foods.

Bulky foods, having little or no nutritive value, are useful in satisfying hunger, relieving constipation, and in serving as a vehicle for the administration of fats to diabetics. These are described under the section of Non-Nutritive Foods.

Since most of the so-called "diabetic foods" on the market possess no specific value in that disease, they are not included under foods for diabetics. Only foods which are metabolized in a manner different from ordinary protein, carbohydrate and fat are here described.

INTARVIN.—An artificial fat made from fatty acids having an odd number of carbon atoms. Intarvin is composed of the glyceryl ester of margaric acid admixed with small quantities of glyceryl esters of pentadecylic, palmitic and stearic acids, 82 per cent; liquid petrolatum, 12 per cent; water, 6 per cent.

Actions and Uses.—Intarvin is proposed for use in diabetes mellitus on the ground that fatty acids containing an odd number of carbon atoms do not yield ketone bodies on oxidation in the normal or in the diabetic organism, and that for this reason it may with advantage replace the natural fats in the diet. The evidence indicates that intarvin does not increase the production and that it may reduce the production of ketones in certain cases; that it has a protein sparing action; that sugar is formed from it in small amounts only; that it has little, if any, beneficial effect on the carbohydrate metabolism in the human organism; that its tallow-like taste is a drawback to its use, and that it may prove useful in the dietary treatment of diabetes in certain cases.

Dosage.—From the total number of calories required for the day, the number supplied by the diet is deducted; the remainder is the number of calories per day to be furnished by intarvin. The caloric value of intarvin is 8 calories per gram—approximately 120 calories per heaping tablespoonful.

Intarvin is best taken in its natural granulated form, followed by a drink of water, tea or coffee. It may also be taken mixed with other food, such as salads, coffee, sweet cream or tomatoes.

Manufactured by the Intarvin Co., Inc., New York. U. S. patent 1,455,254 (May 15, 1923; expires 1940). U. S. trademark 184,860.

Intarvin occurs as white "lumpy" masses, possessing an unctuous feel and an odor and taste resembling those of tallow.

Intarvin is readily soluble in chloroform and ether; insoluble in water. In treating intarvin with hot alcohol, the product dissolves, forming two layers, the alcohol solution being the upper layer and liquid petrolatum being the lower layer.

Boil about 1 Gm. of intarvin with 25 cc. of sodium hydroxide solution: a soap solution results.

Distilled water boiled with intarvin does not acquire an alkaline reaction (*alkalis*).

Dissolve 10 Gm. of intarvin in 30 cc. of chloroform, mix the solution with 10 cc. of neutral alcohol, and add 1 drop of phenolphthalein solution as indicator: not more than 2 cc. of normal sodium hydroxide is required to produce a pink tint after shaking the solution vigorously (*limit of free fatty acid*).

Incinerate about 1 Gm. of intarvin: not more than 0.1 per cent of ash remains.

Transfer about 2 Gm. of intarvin, accurately weighed, to a tared weighing bottle, and dry in a desiccator over sulphuric acid for seventy-two hours: the loss in weight shall not exceed 6 per cent (*limit of moisture*).

Transfer about 5 Gm. of intarvin, accurately weighed, to an Erlenmeyer flask, add 20 cc. of alcohol and 2 cc. of sodium hydroxide solution (1 in 1), connect the flask with a reflux condenser and heat for an hour on the water bath. Remove the condenser and allow the flask to remain on the bath until the alcohol is evaporated and the residue is dry. Dissolve the residue as completely as possible in 40 cc. of water and heat on the bath, shaking frequently. Wash into a separatory funnel, cool and extract with four successive portions of petroleum ether, which are collected in a tared flask. Evaporate the petroleum ether and dry at 100 C.: the amount extracted should not be more than 13 per cent (*limit of liquid petrolatum*).

MERCURY AND MERCURY COMPOUNDS

The early methods of administering mercury were by mouth and by inunction. The oral method continues to be popular, but often causes troublesome gastro-intestinal symptoms. The inunction method obviates the digestive disturbances; but the amount of the drug absorbed cannot be well controlled, and it is often practically impossible to introduce an amount sufficient for syphilis.

In more recent years, the attempt to improve mercurial therapy has been mainly along two lines: the perfection of intramuscular usage and the introduction of the organic compounds.

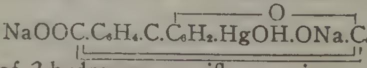
The original practice of injecting mercuric chloride has not gained a wide endorsement because of the pain inflicted and because the necessity of daily injections was difficult to meet. It has been found that the pain is considerably lessened by the use of mercury combined with the amino-acids and their derivatives, such as the succinimide.

The employment of mercurial salts that are less soluble than the bichloride has enabled the physician to give injections at longer intervals and still ensure a daily absorption of the drug. These insoluble preparations, such as the salicylate and the benzoate, are injected into the muscle, but they are accompanied by no little pain.

The organic compounds of mercury, such as mercurol, are said to be less irritating to the gastro-intestinal tract than the inorganic salts. Further experience will be necessary to determine their real value.

Compounds of mercury are also used for preparation of antiseptic and germicidal solutions.

Mercuric Compounds

FLUMERIN-H. W. & D.—Disodium-2-hydroxymercurifluorescin,  $\mathrm{NaOOC\underbrace{.C_6H_4.C.\overbrace{C_6H_2.HgOH.ONa.C}^{O}}_{}{}_6H_3O}$.—The disodium salt of 2-hydroxymercurifluorescein.

Actions and Uses.—Flumerin-H. W. D., when injected intravenously, is tolerated by rabbits in doses containing from eight to twenty times the amount of mercury present in the therapeutic dose of other mercurial drugs commonly used. When injected into rabbits with syphilitic lesions, the drug brings about resolution of the lesions without apparent injury to the kidney.

According to the report of White, Hill, Moore and Young (J. A. M. A. **79**:879 [Sept. 9] 1922), flumerin injected intravenously in man in doses of 3 mg. per Kg. causes the disappearance of spirochetes from primary and secondary syphilitic lesions. According to these authors, flumerin will bring about resolution of the lesions and in about one-half the cases it will change a positive blood Wassermann reaction to negative. In tertiary syphlitic lesions, resolution of the lesions and disappearance of a positive Wassermann reaction was brought about in a majority of the cases treated by White, Hill, Moore and Young. Judging from urinary examination no permanent renal damage was done by the injection of the drug.

Dosage.—From 0.002 to 0.005 Gm. per Kg. of body weight injected intravenously in 2 per cent aqueous solution. Flumerin-H. W. & D. is incompatible with acids, halides and the salts of many alkaloids. Therefore water and not physiologic solution of sodium chloride is used to prepare solutions. If solutions be made with sterile water they may be used during three days if kept in well stoppered bottles in the dark.

Manufactured by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

Flumerin-H. W. & D. Tubes, 0.15 Gm.

Flumerin-H. W. & D. Tubes, 0.20 Gm.

Flumerin-H. W. & D. Tubes, 0.25 Gm.

Flumerin-H. W. & D. Tubes, 0.30 Gm.

Flumerin-H. W. & D. is a red, odorless powder; somewhat hygroscopic. It is soluble in hot water (about 1 in 10); insoluble in alcohol, chloroform or ether. On incineration flumerin-H. W. & D. yields an ash containing sodium carbonate. Aqueous solutions of flumerin-H. W. & D. are deep orange-red in strong concentrations, but show a greenish-red fluorescence in very dilute solutions, the fluorescence being less intense than that of fluorescein in the same concentration. Aqueous solutions of flumerin-H. W. & D. are decomposed by acids, chlorides, bromides, iodides and the salts of many alkaloids, and local anesthetics.

Dissolve 1 Gm. of flumerin-H. W. & D. in 50 cc. of water: no precipitate is produced when separate portions of this solution are treated with sodium hydroxide solution, potassium iodide solution and solution of blood serum. No precipitate is produced when a portion of the 2 per cent aqueous solution is treated with freshly prepared ammonium sulphide solution *(absence of ionic mercury)*, but on standing or on boiling, a suspension or precipitate of mercuric sulphide is produced. To a 2 per cent. solution of flumerin-H. W. & D. add one-half its volume of hydrochloric acid: a precipitate forms. Boil the mixture for one minute, cool, dilute, filter and add ammonium sulphide solution to the filtrate: mercuric sulphide is formed. Add. 1 cc. of a 1 in 1,000 solution of flumerin-H. W. & D. to 1,000 cc. of water: the solution shows a greenish-yellow fluorescence and the color is yellow by transmitted light. Add 1 cc. of iodine solution and stir: an eosin-like color develops immediately and the solution is pink by transmitted light (*identification of the fluorescein nucleus*).

Determine the chloride content of flumerin-H. W. & D. by ignition with lime and precipitation of the chloride as silver chloride in the usual way: not more than 0.2 per cent of chlorine is found. (*Absence of excessive amounts of salts of chloromercurifluorescein.*)

Dissolve about 1 Gm. of flumerin-H. W. & D., accurately weighed, in about 50 cc. of water at 50-60 C., filter through a weighed Gooch crucible, wash the residue thoroughly until the washings have only a slight color, dry at 110 C. and weigh: no weighable residue is found. Place about 0.2 Gm. of finely powdered flumerin-H. W. & D., accurately weighed, in an 800 cc. Kjeldahl flask and slowly add 10 cc. of sulphuric acid, in such a way as to wash down any adherent particles. Mix the materials carefully, heat to a temperature of from 60 to 75 C., remove the flame and add, little by little, finely powdered potassium permanganate, mixing thoroughly after each addition, until the presence of a considerable excess of brown manganese compounds is noted. The appearance of a slight flame after the addition of each portion of the oxidizing agent is immaterial. Cool the mixture to room temperature, add 100 cc. of water, then gradually add powdered oxalic acid with shaking until the solution becomes clear. Filter if necessary, make the volume to about 200 cc. with water, pass in hydrogen sulphide, collect the precipitate in a Gooch crucible, wash it successively with water containing hydrogen sulphide, alcohol, ether, carbon disulphide and ether, dry at 100 C. and weigh: the weight of mercuric sulphide corresponds to not less than 30 per cent of mercury.

MERCURIC BENZOATE.—Hydrargyri Benzoas.—Hydrargyrum Benzoicum. — $Hg(C_6H_5COO)_2+H_2O$. — The mercuric salt of benzoic acid.

Actions and Uses.—The same as those of mercuric chloride.

Dosage.—Mercuric benzoate is used for intramuscular injections in syphilis and in treating gonorrhea. In urethral cases, the solution may be 1 in 2,000 or 1 in 1,000 with an equal quantity of sodium chloride. For intramuscular injection, mercuric benzoate is given in a 1 per cent solution by dissolving 0.3 Gm. of mercuric benzoate in 30 cc. of water, containing 1.5 Gm. of ammonium benzoate or given in 2 per cent solution with 2.5 per cent of sodium chloride, the average dose being about 24 or 12 minims, respectively (0.015 Gm., ¼ grain), every second day

Sterile Ampoules Mercury Benzoate 2 per cent., 1 Cc.: Mercuric benzoate-N. N. R., 0.02 Gm. (⅓ grain), in a solution of sodium chloride, 2.5 per cent, 1 cc.

Prepared by Swan-Myers Company, Indianapolis.

Mercuric benzoate is a white, crystalline powder; slightly soluble in water, yielding a weakly acid solution; more soluble in an aqueous sodium chloride solution. It is insoluble in alcohol or ether. At 20 C., a 10 per cent solution of sodium benzoate dissolves 1 per cent of its weight of mercuric benzoate. With alcohol mercuric benzoate is decomposed into a basic salt having a yellow color.

A solution of 1 Gm. of mercuric benzoate and 0.5 Gm. of sodium chloride in 20 cc. of water yields a black precipitate with hydrogen sulphide, and with ferric chloride solution, it yields a fawn-colored precipitate of ferric benzoate.

Shake 1 Gm. of mercuric benzoate with 20 cc. of water and filter: no turbidity is produced when silver nitrate solution is added to 10 cc. of the filtrate acidified with a few drops of nitric acid (*chloride*). Two cc. of a similar solution, when mixed with ferrous sulphate solution to which is added sulphuric acid so as to form a layer beneath, should produce no brown coloration at the zone of contact of the two solutions (*nitrates*).

Incinerate about 0.5 Gm. of the salt in a porcelain crucible: not more than 0.1 per cent of residue remains.

Mercury Benzoate-Merck.—A brand of mercuric benzoate-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributors. No U. S. patent or trademark.

Mercury (Mercuric) Benzoate-Seydel.—A brand of mercuric benzoate-N. N. R.

Manufactured by The Seydel Chemical Company, Jersey City, N. J. No U. S. patent or trademark.

MERCURIC CYANIDE.—Hydrargyri Cyanidum.—Hydrargyrum Cyanatum.—$Hg(CN)_2$.—The mercuric salt of hydrocyanic acid.

Actions and Uses.—Mercuric cyanide has been reported to be as actively antiseptic as mercuric chloride and to be less irritating; but this has been questioned. It is used locally and internally as is mercuric chloride. Blum and Schwab (*Presse Med.* **30**:1081 [Dec. 16] 1922) highly recommended this drug as a diuretic in cardiac (but not in renal) disease. They give it in doses of 0.04 to 0.05 Gm. by intravenous or intramuscular injection. They state, however, that mercury should be used as a diuretic only as a last resort when other drugs have failed.

Dosage.—Internally, from 0.004 to 0.008 Gm. (1/16 to 1/8 grain); locally, solutions of from 1 in 4,000 to 1 in 2,000 may be used for applications to the eye or mucous membranes; from 25 to 35 minims of a 1 per cent solution may be used hypodermically without causing local irritation. Death has occurred from the use of a vaginal injection containing 0.9 Gm. (14 grains) of mercuric cyanide.

In diphtheria and croup, it is used in 0.01 per cent solution as a gargle or internally in doses of from 0.0005 Gm. to 0.001 Gm. (0.0077 to 0.0154 grain). In fibrinous rhinitis it is used on a tampon in 0.04 per cent solution.

Mercuric cyanide occurs in colorless or white, prismatic crystals, or white powder, odorless and having a bitter, metallic taste (the salt is exceedingly poisonous). It is darkened on exposure to light; is soluble at 15 C. in 12.8 parts of water and in 15 parts of alcohol, in 3 parts of boiling water and in 6 parts of boiling alcohol, and is very sparingly soluble in ether.

When slowly heated in a glass tube, the salt decrepitates and decomposes into metallic mercury and inflammable cyanogen gas, which burns with a purple flame. On further heating, the blackish residue, consisting of paracyanogen with globules of metallic mercury, is wholly dissipated. If 1 part of the salt is gently heated with 1 part of iodine in a dry test-tube it will produce at first a yellow sublimate, which afterward becomes red, and above this a sublimate of colorless, needle-shaped crystals. On adding hydrochloric acid to the aqueous solution of the salt, the odor of hydrocyanic acid is evolved. A 5 per cent aqueous solution of the salt should be neutral to litmus paper, and should not yield, on the gradual addition of a few drops of potassium iodide solution, either a red or a reddish precipitate, soluble in an excess of the precipitant, nor should it yield a white precipitate with silver nitrate solution (*mercuric chloride*). If mercuric cyanide is dissolved in an aqueous solution of sodium chloride, the addition of phenolphthalein to this solution should produce no red coloration (*mercuric oxide*). Ammonia should not color an aqueous solution blue (*mercuric oxide*). Ammonia water dissolves mercuric cyanide without producing a white precipitate (*oxycyanide*).

Mercuric Cyanide-Mallinckrodt.—A brand of mercuric cyanide-N. N. R.

Manufactured by the Mallinckrodt Chemical Works, St. Louis. No U. S. patent or trademark.

Mercury Cyanide-Merck.—A brand of mercuric cyanide-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

MERCURIC OXYCYANIDE.—Hydrargyri Oxycyanidum.—Hydrargyrum Oxycyanatum.—$Hg(CN)_2HgO$.—A basic-mercuric salt of hydrocyanic acid, containing from 51.7 to 56.0 per cent of mercuric cyanide [$Hg(CN)_2$] and from 44.3 to 48.0 per cent of mercuric oxide (HgO).

Actions and Uses.—Mercuric oxycyanide has been proposed as a substitute for mercuric chloride. Its antiseptic power is claimed to be greater and it is asserted to be less irritating than mercuric chloride because it does not act on albumin to the same extent. It has the advantage over mercuric chloride in that it does not corrode steel instruments.

Representative syphilographers differ as to the use of mercuric oxycyanide intravenously. Some believe that its use should be limited to hospitals; others, that it has no advantage over other and safer methods of administering mercury; while others consider it safe and valuable; but all are in accord that its safe use requires experience.

Dosage.—Mercuric oxycyanide may be administered in the same doses as mercuric chloride. It may be applied locally in solutions of 1 in 5,000 or somewhat stronger.

Sterile Ampules of Mercury Oxycyanide, 0.008 Gm.: Each contains 5 cc. of solution, representing 0.008 Gm. (⅛ grain) of mercuric oxycyanide-N. N. R.

Prepared by the Swan-Myers Co., Indianapolis.

Sterile Ampules Mercury Oxycyanide, 0.016 Gm.: Each contains 5 cc. of solution representing 0.016 Gm. (¼ grain) of mercuric oxycyanide-N. N. R.

Prepared by the Swan-Myers Co., Indianapolis.

Sterile Ampules of Mercury Oxycyanide 0.01 Gm.: Each contains 5 cc. of solution, representing 0.01 Gm. (⅙ grain) of mercuric oxycyanide-N. N. R.

Prepared by the Swan-Myers Co., Indianapolis.

Mercuric oxycyanide occurs as a white, or nearly white, microcrystalline powder, soluble in about 80 parts of water, yielding a solution alkaline to litmus. Boiled with a mixture of sodium hydroxide, ferrous sulphate and ferric chloride solutions, cooled and then treated with hydrochloric acid, mercuric oxycyanide yields a blue precipitate. A saturated solution yields a white precipitate with ammonium chloride, soluble in an excess of the precipitant. Tannic acid solution produces at first a deep yellow color, then gradually a tan colored precipitate. Hydrogen sulphide, and ammonium sulphide both produce a black precipitate in an aqueous solution of mercuric oxycyanide. Potassium iodide solution when added to a solution of mercuric oxycyanide yields a red precipitate soluble in excess of the iodide. An aqueous solution should not respond to tests for chloride, nor should 0.2 Gm. leave a weighable residue when ignited.

Dissolve about 0.5 Gm. of mercury oxycyanide, accurately weighed, in 50 cc. of warm water, together with 0.5 Gm. of sodium chloride, cool the solution, add methyl orange and titrate with tenth-normal hydrochloric acid to the red-end point. Add 2 Gm. of potassium iodide, dilute with water to about 150 cc. and titrate again with the tenth-normal acid to the red-end point: in the first titration, each cubic centimeter of tenth-normal hydrochloric acid solution is equivalent to 0.01083 Gm. of HgO and in the second, each cubic centimeter of tenth-normal hydrochloric acid solution is equivalent to 0.012631 Gm. of $Hg(CN)_2$.

MERCURIC SALICYLATE.—For description see the U. S. Pharmacopeia and Useful Drugs under Hydrargyri Salicylas.

Ampules Mercuric Salicylate-Squibb, 0.065 Gm.: Each ampule contains mercuric salicylate 0.065 Gm. (1 grain) suspended in 1 cc. of an emulsion of wool fat and almond oil with quinine and urea hydrochloride, 0.25 per cent added as a local anesthetic.

Prepared by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

Compressible Capsules Mercury Salicylate-S. D. C., 1 grain, for Intramuscular Injection: Each capsule contains mercuric salicylate, 0.065 Gm. (1 grain) suspended in 1 cc. of a mixture of benzoinated lard, 67 per cent; peach kernel oil, 31 per cent; camphor, 1 per cent; phenol, 1 per cent.

Prepared by the Synthetic Drug Company, Toronto, Canada.

Compressible Capsules Mercury Salicylate-S. D. C., 1½ grains, for Intramuscular Injection: Each capsule contains mercuric salicylate, 0.1 Gm. (1½ grains) suspended in 1 cc. of a mixture of benzoinated lard, 67 per cent; peach kernel oil, 31 per cent; camphor, 1 per cent; phenol, 1 per cent.

Prepared by the Synthetic Drug Company, Toronto, Caanda.

Compressible Capsules Mercury Salicylate-S. D. C., 2 grains, for Intramuscular Injection: Each capsule contains mercuric salicylate, 0.13 Gm. (2 grains) suspended in 1 cc. of a mixture of benzoinated lard, 67 per cent; peach kernel oil, 31 per cent; camphor, 1 per cent; phenol, 1 per cent.

Prepared by the Synthetic Drug Company, Toronto, Canada.

Glaseptic Ampoules Mercury Salicylate-P. D. & Co., 0.065 Gm. (1 grain): Each cubic centimeter contains mercuric salicylate, 0.065 Gm.; apothesine, 0.01 Gm.; in olive oil, 1 cc.

Prepared by Parke, Davis & Co., Detroit.

Glaseptic Ampoules Mercury Salicylate-P. D. & Co., 0.13 Gm. (2 grains): Each cubic centimeter contains mercuric salicylate, 0.13 Gm.; apothesine, 0.01 Gm.; in olive oil, 1 cc.

Prepared by Parke, Davis & Co., Detroit.

Sterile Ampoules Mercury Salicylate 0.065 Gm. (1 grain): Each ampule contains mercuric salicylate ethyl aminobenzoate, 0.065 Gm.; 0.02 Gm., in neutral vegetable oil, 1 cc. Each ampule contains more than 1 cc. of suspension.

Prepared by Swan-Myers Company, Indianapolis.

Sterile Ampoules Mercury Salicylate 0.097 Gm. (1½ grain): Each ampule contains mercuric salicylate 0.097 Gm.; ethyl aminobenzoate, 0.02 Gm., in neutral vegetable oil, 1 cc. Each ampule contains more than 1 cc. of suspension.

Prepared by Swan-Myers Company, Indianapolis.

Sterile Ampules of Mercury Salicylate-H. W. & D., 1 grain: One cc. of suspension contains 0.06 Gm. (1 grain) of mercuric salicylate. Each ampule contains more than 1 cc. of suspension. Mercuric salicylate is suspended in a mixture of vegetable fats which are solid at 34.4 C., but liquid at body temperature. For use, the ampule is immersed in warm water until the fat is liquefied, agitated, opened, and a measured quantity of the contents injected through a 20-gage needle. This preparation should not be injected intravenously.

Prepared by Hynson, Westcott & Dunning, Baltimore, Md. No U. S. patent or trademark.

Sterile Ampules of Mercury Salicylate-H. W. & D., 1½ grains.: One cc. of suspension contains 0.09 Gm. (1½ grains) of mercuric salicylate.

Each ampule contains more than 1 cc. of suspension. Mercuric salicylate is suspended in a mixture of vegetable fats which are solid at 34.4 C., but liquid at body temperature. For use, the ampule is immersed in warm water until the fat is liquefied, agitated, opened, and a measured quantity of the contents injected through a 20-gage needle. This preparation should not be injected intravenously.

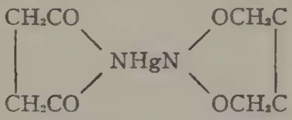
Prepared by Hynson, Westcott & Dunning, Baltimore, Md. No U. S. patent or trademark.

Sterile Ampules of Mercury Salicylate-H. W. & D., 2 grains: One cc. of suspension contains 0.12 Gm. (2 grains) of mercuric salicylate. Mercuric salicylate is suspended in a mixture of vegetable fats which are solid at 34.4 C., but liquid at body temperature. For use, the ampule is immersed in warm water until the fat is liquefied, agitated, opened, and a measured quantity of the contents injected through a 20-gage needle. This preparation should not be injected intravenously.

Prepared by Hynson, Westcott & Dunning, Baltimore, Md. No U. S patent or trademark.

MERCURIC SUCCINIMIDE.—**Hydrargyri Succinimidum.**

—$Hg[(CH_2CO)_2N]_2$.—The mercuric salt of succinic acid-imide,



Actions and Uses.—Mercuric succinimide has the action of other salts of mercury, but its solutions are said to be relatively nonirritating. The preparation is used as are other compounds of mercury in the treatment of syphilis.

Dosage.—Mercuric succinimide is used mainly by hypodermic injection. The daily hypodermic dose is from 0.01 to 0.02 Gm. (⅙ to ⅓ grain) given in the form of a 2.5 per cent solution (from 0.5 to 1 cc., or 8 to 16 minims of such solution).—Mercuric succinimide may be given by the mouth in doses of from 0.01 to 0.015 Gm. (⅙ to ¼ grain).

Ampuls Mercury Succinimide-Mulford, ⅙ grain.

Prepared by H. K. Mulford Co., Philadelphia.

Glaseptic Ampoules Mercury Succinimide-P. D. & Co., 0.01 Gm. (⅙ grain): Each cubic centimeter contains mercuric succinimide-N. N. R., 0.01 Gm.; apothesine, 0.005 Gm.; in physiological solution of sodium chloride, 1 cc.

Prepared by Parke, Davis & Co., Detroit.

Hypodermic Tablets No. 50 Mercuric Succinimide-Mulford, 0.012 Gm (⅙ grain).

Prepared by H. K. Mulford Co., Philadelphia.

Sterile Ampoules Mercury Succinimide 0.01 Gm. (⅙ grain): **mercuric succinimide-N. N. R., 0.01 Gm., in water, 1 cc.**

Prepared by Swan-Myers Company, Indianapolis.

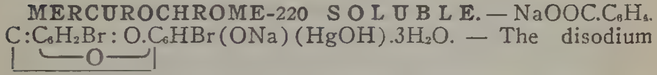
Mercuric succinimide is a white crystalline powder; soluble in about 20 parts of cold water; soluble in about 5 parts of boiling water, and in 300 parts of alcohol. It is very stable in solution. The aqueous solution is not affected by albumin. Mercuric succinimide should be protected from light. Toward hydrogen sulphide and potassium iodide it reacts as an inorganic mercuric compound. Addition of sodium hydroxide solution to a aqueous solution of mercuric succinimide produces a yellowish-white precipitate, which on heating is reduced to metallic mercury. If mercuric succinimide is heated with five times its bulk of zinc dust, pyrrol is given off, which may be recognized by the red color which is developed when a pine shaving moistened with hydrochloric acid is held in its vapors.

The aqueous solution must be neutral and should not be affected by solutions of silver nitrate or egg albumin (*absence of mercuric chloride and other mercuric salts*).

Incinerate about 0.5 Gm. of the salt in a porcelain crucible: not more than 0.1 per cent of residue remains. If 1 Gm. is shaken with 10 cc. of anhydrous ether, the liquid filtered and the ether removed by evaporation, no weighable residue should remain. If 1 Gm. is suspended in ether and hydrogen sulphide passed through the mixture for some time, the mercury succinimide will be decomposed, the mercury being precipitated as mercuric sulphide. If the ether is filtered from this precipitate, and evaporated, a residue of succinimide will remain which should have a melting-point of from 124 to 125 C.

Mercury Succinimide-Merck.—A brand of mercuric succinimide-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.



MERCUROCHROME-220 SOLUBLE.—$NaOOC.C_6H_4.C{:}C_6H_2Br{:}O.C_6HBr(ONa)(HgOH).3H_2O$.—The disodium salt of 2:7-dibromo-4-hydroxymercurifluorescein, containing 24 to 26 per cent of mercury.

Actions and Uses.—Mercurochrome-220 soluble is a strong and rapidly acting germicide; it is active in urine, a 1 in 1,000 solution killing *Bacillus coli* and *Staphylococcus aureus* in this medium in one minute. It penetrates the tissues readily. The drug is tolerated in a strength of 1 per cent by the bladder, renal pelvis and urethra; a 2.5 per cent solution applied to the anterior urethra causes only temporary discomfort. The toxicity, when tested by intravenous injection into rabbits is rather high, 10 mg. per Kg., invariably causing death within 24 hours and 5 mg. causing a decrease in phenolsulphonphthalein output and an albuminuria which lasts about a week. Dogs are more resistant. No systemic effects have been observed following its local application in the human. Mercurochrome-220 soluble has been used in cystitis and urethritis and in chancroidal ulcerations; also in affections of the eye and ear, such as ophthalmia neonatorum and otitis media. The drug has also been injected intravenously in the treatment of septicemias and of local infections (subcutaneous abscesses following severe injury, retroperitoneal abscess following bladder instrumentation, etc.). The drug seems to be particularly active against organisms of the colon group; although it has seemed to give good results in some cases of staphylococcus and streptococcus septicemia, it is often times without effect. The intravenous injection is usually but not invariably followed by a transient increase of temperature and vomiting and sometimes by a severe diarrhea.

Dosage.—In the treatment of infections of the kidney pelvis, the ureters are catheterized and the pelvis gently filled with a

1 per cent solution; the catheter is plugged and the solution retained for five minutes. In the treatment of bladder conditions, one ounce of the 1 per cent solution is introduced into the bladder and retained for one hour or longer, the treatment being given daily or on alternate days, or at longer intervals according to circumstances. In anterior gonococcus urethritis, the anterior urethra is filled with a 1 per cent solution and the solution retained for five minutes. If the posterior urethra be involved, the solution is gently retained for an hour or more. In rare cases, considerable irritation is produced, particularly in those with residual urine. Later, in the treatment of acute anterior gonorrhea, a 2.5 per cent solution is used every three hours. In chancroidal ulcerations, the drug is applied as a moist dressing (1 per cent) or as a starch paste (5 per cent) or as an ointment (5 per cent). The results have been satisfactory and no untoward effects observed. In ophthalmia neonatorum a 2.5 per cent solution is freely instilled in each eye several times a day. The dose by intravenous injection has usually been 5 mg. per Kg. of body weight. This dosage is administered in a one per cent solution, freshly prepared from recently distilled water and filtered before using. It is equal to 23 cc. of a 1 per cent solution per 100 pounds of body weight. Solutions are self-sterilizing and should not be boiled. They should be made up from the drug itself, as the tablets are not suitable for this purpose.

Mercurochrome-220 soluble is incompatible with acids, with the salts of most alkaloids and with most local anesthetics. The aqueous solution stains the skin red but the discoloration may be removed by a washing in a solution of sodium hypochlorite (solution of chlorinated soda).

Manufactured by Hynson, Westcott & Dunning, Baltimore, by license of E. C. White, U. S. patent 1,535,003 (April 21, 1925; expires 1942). U. S. trademark 197,189.

Sealed Tubes Mercurochrome-220 Soluble, 0.5 Gm.

Tablets of Mercurochrome-220 Soluble: Each contains 4.6 grains.

Mercurochrome-220 soluble occurs as iridescent, green scales or granules; odorless; permanent in the air. It is freely soluble in water; practically insoluble in alcohol; insoluble in chloroform or ether. On incineration mercurochrome-220 soluble yields an ash containing sodium bromide and sodium carbonate.

The aqueous solution (1 in 10) of mercurochrome-220 soluble is of a deep cherry-red color; on dilution with water it becomes fluorescent. The aqueous solution is stable in the air, does not precipitate proteins and does not respond to the usual tests for mercury ions. Add a few drops of hydrochloric acid to about 10 cc. of an aqueous solution of mercurochrome-220 soluble (1 in 100): an orange-red precipitate is given and, if the mixture be filtered, the filtrate is nearly colorless, or only slightly yellow.

Dry about 1 Gm. of mercurochrome-220 soluble, accurately weighed, to constant weight over sulphuric acid: the loss does not exceed 10 per cent. Dissolve about 1 Gm. of mercurochrome-220 soluble, accurately weighed, in about 50 cc. of water at 50-60 C., filter through a weighed Gooch crucible, wash the residue thoroughly until the washings have only a slight color, dry at 110 C. and weigh: the insoluble matter amounts to not more than 0.2 per cent of the weight taken. Place about 0.2 Gm. of finely powdered mercurochrome-220 soluble, dried to constant weight over sulphuric acid, accurately weighed, in an 800 cc. Kjeldahl flask and slowly add 10 cc. of sulphuric acid, in such a way as to wash down any adherent particles. Mix the materials carefully, heat to a temperature of from 60 to 75 C., remove the flame and add, little by little, finely powdered potassium permanganate, mixing thoroughly after each addition, until the presence of a considerable excess of brown manganese compounds is noted. The appearance of a slight flame after the addition of each portion of the oxidizing agent is immaterial. Cool the mixture to room temperature, add 100 cc. of water, then gradually add powdered oxalic acid with shaking until the solution becomes clear. Filter if necessary, make the volume to about 200 cc. with water, pass in hydrogen sulphide, collect the precipitate in a Gooch crucible, dry at 100 C. and weigh: the weight of mercuric sulphide corresponds to not less than 24 or more than 26 per cent of mercury.

Saf-T-Top Mercurochrome Solution: An aqueous 2 per cent solution of mercurochrome-220 soluble marketed in ampules having a capillary opening, containing 2 cc.

Prepared by Robert A. Bernhard, Rochester, N. Y.

MERCUROL.—Hydrargyri Nucleinas.—Mercury Nucleinate.—An organic compound of mercury with nucleinic acid from yeast, containing 20 per cent of metallic mercury.

Actions and Uses.—Mercurol does not coagulate albumin; it has marked bactericidal power and possesses the pharmacologic action of soluble mercury compounds.

It is said to be useful as a local antiseptic application and as an antisyphilitic remedy.

Dosage.—From 0.03 to 0.12 Gm. (½ to 2 grains). It is supplied only in the form of mercurol and iodalbin tablets. (See under Iodalbin.)

Manufactured by Parke, Davis & Company, Detroit. U. S. patent 637,355 (expired).

Mercurol is prepared by adding a solution of mercuric chloride to an alkaline solution of nuclein, containing an excess of alkali, precipitating the resulting nucleinate of mercury by the addition of alcohol and a concentrated solution of a neutral salt (sodium chloride), separating the precipitate, washing and drying it.

It is a brownish-white powder, soluble in water, especially in warm water, insoluble in alcohol. Its watery solution has a distinct metallic taste, a weak alkaline reaction, and is not precipitated by alkalis, nor by albuminous liquids.

The mercury in this preparation resists the action of hydrogen sulphide to a marked degree.

MERCUROSAL.—Disodiumhydroxymercurisalicyloxyacetate.—$(HOHg).NaOOC.C_6H_3.OCH_2COONa$. Mercurosal contains from 43.0 to 43.8 per cent of mercury in organic combination.

Actions and Uses.—It is claimed that mercurosal is relatively free from irritant action, that it is eliminated without untoward effect on the kidney and that its toxicity is relatively lower than that of mercuric chloride and mercuric salicylate. Mercurosal is intended for the mercurial treatment of syphilis. It is administered either intramuscularly or intravenously. The Council accepted mercurosal as a comparatively non-toxic, comparatively non-irritating mercury salt which does not precipitate protein.

Dosage.—The usual intramuscular dose is 0.05 Gm. dissolved in 2 cc. of sterile water every fourth or fifth day for ten or twelve doses. The usual intravenous dose is 0.1 Gm. dissolved in 5 cc. of sterile water administered every second or third day for ten or twelve doses.

Manufactured by Parke, Davis and Co., Detroit, Mich. U. S. patent 1,513,115 (Oct. 28, 1924; expires 1941). U. S. trademark 161,254.

Mercurosal Ampoules 0.1 Gm.: Mercurosal, 0.1 Gm., in distilled water, containing 0.1 per cent of sodium citrate, 5 cc.

Mercurosal ℞ 1 (Intravenous): sealed tubes containing mercurosal 0.1 Gm.

Mercurosal ℞ 2 (Intramuscular): sealed tubes containing mercurosal 0.05 Gm.

Mercurosal Solution: Each cubic centimeter contains mercurosal, 0.025 Gm. (5⁄13 grain), in distilled water containing 0.1 per cent of sodium citrate.

Mercurosal is a white, amorphous powder. It is soluble in about 10 parts of water, insoluble in the usual organic solvents. Dilute aqueous solutions of mercurosal are quite stable when protected from air, but on prolonged standing may give rise to an insoluble compound. Mercurosal is decomposed by acids, and by strong reducing agents; salts of heavy metals, such as silver or lead, yield insoluble precipitates. From a 1 to 2 per cent aqueous solution of mercurosal, calcium chloride precipitates a calcium salt which dissolves on subsequent dilution with water.

Mercurosal is faintly alkaline to phenolphthalein solution. When an aqueous solution of mercurosal is treated with an alkali hydroxide, a clear solution results. No precipitate is produced when an aqueous solution of mercurosal is saturated with carbon dioxide. When an aqueous solution of mercurosal is acidified with acetic acid or with mineral acids, a white precipitate is produced.

Heat mercurosal, 1 Gm., with hydrochloric acid (1 in 1), 25 cc. until decomposition has taken place, cool and collect the precipitate; dissolve the precipitate in alkali, filter, reprecipitate, and crystallize from water: these crystals melt at 192 C. (*salicylacetic acid*). Treat an aqueous solution of mercurosal with iodine solution, acidify with hydrochloric acid and collect the precipitate; after drying, the precipitate melts at 217 C. Saturate an aqueous solution of mercurosal with hydrogen sulphide: no precipitate is produced (*absence of "inorganic" mercury).*

Dry mercurosal at 100 C. for one hour: the loss does not exceed 1 per cent. Dissolve about 0.4 Gm. of dried mercurosal, accurately weighed, in water 5 cc.; add concentrated hydrochloric acid, 5 cc.; cover the beaker and digest on a steam bath until solution takes place; dilute to from 100 to 125 cc. with water and saturate with hydrogen sulphide; collect the precipitate in a tared gooch crucible; wash successively with water, alcohol and ether; dry to constant weight at 100 C.: the weight of mercuric sulphide corresponds to from 43 to 43.8 per cent of mercury.

MERGAL.—A mixture of 1 part of mercuric cholate and 2 parts of albumin tannate put up in capsules. Each capsule is said to contain approximately 0.15 Gm. (2¼ grains) of mergal, equivalent to 0.05 Gm. (¾ grain) of mercuric cholate and 0.1 Gm. (1½ grains) of albumin tannate. Mergal contains approximately 4.4 per cent of mercury.

Actions and Uses.—Mergal is said to pass through the stomach without decomposition and to be decomposed into its constituents in the small intestine, where the mercury is quickly absorbed into the blood and excreted through the kidneys. It is said to be useful in all forms of syphilis and in the so-called parasyphilitic affections, such as tabes and general paralysis. It is also said to be useful for the intermittent treatment according to the method of Fournier and Neisser.

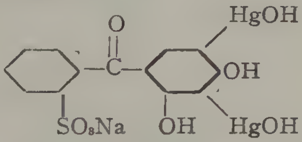
Dosage.—One capsule, three times a day after meals, gradually increasing to 2 capsules, five or six times a day.

Manufactured by J. D. Riedel Aktiengesellschaft, Berlin, Germany (Riedel & Co., Brooklyn). U. S. patent 811,193 (Jan. 30, 1906; expired). U. S. trademark 53,919.

Mergal is a yellowish-white, loose, somewhat light powder, insoluble in water and alcohol and almost insoluble in solution of sodium chloride.

When 0.1 Gm. of mergal is shaken with a few drops of saturated solution of cane sugar and underlaid with concentrated sulphuric acid, a purplish-red to reddish-violet zone is produced. If 0.2 Gm. of mergal is warmed on the water bath with 10 cc. of hydrochloric acid for about fifteen minutes and the evaporated water replaced after cooling and filtering, there results a colorless or slightly yellowish solution, which gives a black precipitate with solution of hydrogen sulphide. The same filtrate gives, with a drop of stannous chloride solution, an immediate precipitation of metallic mercury. Mergal should leave no weighable residue on incineration. Two-tenths Gm. of mergal boiled for one minute with 20 cc. of water gives a clear filtrate which is colored dark violet on the addition of a drop of solution of ferric chloride. One-tenth gram of mergal when heated to boiling with a mixture of 5 cc. of concentrated sulphuric acid and 5 cc. of water produces a turbid reddish solution. The filtrate after dilution with 3 or 4 parts of water and the addition of a drop of solution of copper sulphate gives on careful underlaying or on mixture with an excess of sodium hydroxide solution an evanescent violet red color. Mergal should be protected from the light.

MEROXYL.—A mixture containing approximately 50 per cent of the sodium salt of 2,4-dihydroxy-3,5-dihydrox-mercuri-benzophenone-2′-sulphonic acid,



with foreign matter consisting of ammonium 2,4-dihydroxy-benzophenone-2-sulphonate, sodium acetate and water.

Actions and Uses.—A local antiseptic and germicide recommended for superficial infections by Young, White, Hill and Davis (*Surgery, Gynecology and Obstetrics* **36**:508 [April] 1923). It is used for wet dressings of wounds, and also for irrigation of wounds and of infected bladders. When injected intravenously in animals, the toxicity was found to be high; by oral administration, however, the drug showed a much lower degree of toxicity.

Dosage.—For wet dressing of wounds and irrigation of infected wounds, a 0.1 per cent solution is used. For prophylactic treatment of urinary infection, postoperative cystitis, acute gonorrhea, abscess and carbuncle, a 0.5 per cent solution is employed. Solutions of 2.5 per cent or greater strength gelatinize on standing.

Manufactured by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

Meroxyl Tablets-H. W. & D.: Each tablet contains meroxyl, 0.15 Gm. (2.3 grains).

Meroxyl occurs as a flesh colored or pink powder easily soluble in hot water up to 10 per cent. Solutions of 2.5 per cent or stronger gel or form a deposit on cooling. The color of the solution varies with concentration; a 0.5 per cent solution has a brownish pink color with greenish fluorescence, the color becoming browner in more concentrated solutions. The solution produces no stain on skin or fabrics.

Add 1 cc. of sodium hydroxide solution to 1 cc. of meroxyl solution, 1 per cent: no precipitate forms. Add 1 cc. of potassium iodide solution to 10 cc. of meroxyl solution, 1 per cent: no precipitate forms. (If the solution is made neutral or slightly acid with acetic acid, a precipitate is formed.) Add 1 cc. of ammonium sulphide solution to 5 cc. of meroxyl solution, 1 per cent: a black precipitate of mercuric sulphide occurs. Add 3 cc. of sodium hydroxide solution to 3 cc. of meroxyl solution, 10 per cent; the odor of ammonia develops. Add a few drops of diazotized paranitraniline to 2 cc. of a slightly alkaline solution of meroxyl, 0.5 per cent: an intense bordeaux color appears. Add a few drops of a sodium hypochlorite solution to 2 cc. of meroxyl solution, 0.5 per cent: an intense orange color is produced and a fine flaky precipitate forms slowly.

Treat 1 Gm. of meroxyl with 50 cc. of boiling water: (the insoluble matter does not exceed 0.1 per cent).

Assay the product according to the method given under mercurochrome-220 soluble: the mercury content is not less than 26 per cent, nor more than 29 per cent.

MERTHIOLATE.—Sodium Ethylmercuri Thiosalicylate. —$C_2H_5.Hg.S.C_6H_4.COONa$. Merthiolate contains from 49.15 to 49.65 per cent of mercury in organic combination.

Actions and Uses.—Merthiolate, Lilly, is a potent germicide for spore-bearing and non-spore-bearing bacteria. It is used for sterilizing tissue surfaces. It does not precipitate with serum proteins. Merthiolate is much less toxic than mercuric chloride. Rabbits tolerated intravenous doses of 0.020 Gm. to 0.025 Gm. per Kg., and rats as much as 0.045 Gm. when injected slowly, the animals being observed in both cases for seven days. Hemolytic tests with washed rabbit red blood cells indicate that merthiolate has relatively low hemolytic activity.

Dosage.—The concentration recommended for general application is 1 in 1,000 isotonic solution. For hypersensitive mucous membranes, dilutions of from 1 in 2,000 to 1 in 5,000 may be used.

Manufactured by Eli Lilly & Company, Indianapolis, Ind. U. S. patent 1,672,615 (June 5, 1928; expires 1945). U. S. trademark 252,182.

Merthiolate Solution 1:1,000: One gram of merthiolate in 1,000 cc. of water, buffered with 1.4 Gm. of sodium borate in 1,000 cc. and containing sodium chloride to make the solution approximately isotonic.

Merthiolate occurs as a light cream colored nonhygroscopic crystalline powder, having a slight odor. It is stable in air but unstable in sunlight. One part by weight of merthiolate dissolves in approximately 1 part of water or in approximately 8 parts of 95 per cent alcohol. It is practically insoluble in ether and benzene. A 1 per cent solution in water has a *p*H value of about 6.7. A 1 per cent solution is compatible with solutions of procaine and ephedrine salts.

Add diluted sulphuric acid to a solution of merthiolate: a white precipitate of ethylmercurithiosalicylic acid is produced. Recrystallize this product from 95 per cent alcohol and dry in a vacuum over sulphuric acid; it melts at 111-114 C. Bubble carbon dioxide into a 1 per cent solution of merthiolate: a precipitate is produced which is soluble in sodium hydroxide. Add a few drops of silver nitrate solution to a

1 per cent solution of merthiolate: a white precipitate separates. Add a few drops of lead acetate solution to a 1 per cent solution of merthiolate: a white precipitate separates. Add a few drops of copper sulphate solution to a 1 per cent solution of merthiolate: a green precipitate separates.

Shake 0.5 Gm. of merthiolate, accurately weighed, with 20 cc. of anhydrous ether for ten minutes; filter, evaporate the ether, dry in a vacuum over sulphuric acid to constant weight: the weight of the residue does not exceed 0.003 Gm. Dissolve about 0.2 Gm. of merthiolate in 5 cc. of sulphuric acid: not more than a slight yellow color is produced. Mix equal parts of a 1 per cent solution of merthiolate and ammonium sulphide: a white precipitate is formed, but no blackening occurs after standing forty-eight hours. Dry 0.1 Gm. of merthiolate to constant weight in a vacuum over sulphuric acid: it does not lose more than 0.5 per cent in weight.

Transfer to a platinum dish about 1 Gm. of merthiolate, accurately weighed; add 3 cc. of sulphuric acid and evaporate; add 2 cc. of sulphuric acid and evaporate; add 2 cc. of sulphuric acid and evaporate; introduce into the dish a small piece of ammonium carbonate and heat until it is volatilized, cool in a desiccator and weigh: The sodium is not less than 5.1 per cent nor more than 5.7 per cent. Transfer about 0.2 Gm. of merthiolate, accurately weighed, to a 100 cc. Erlenmeyer flask; add 3 cc. of sodium hydroxide solution, 10 cc. of water, 20 cc. of sodium sulphide (50 Gm. crystals dissolved and diluted to make 100 cc.) and 0.25 Gm. of sodium hydrosulphite; boil under a reflux for twenty minutes; transfer to a weighed platinum dish, dilute to 105 cc., and electrolyze at 4 volts for seventeen hours; remove the solution; wash the dish with water; dry the dish by evaporating the ether, after washing it with alcohol and then ether; weigh: the mercury is equivalent to not less than 49.1 per cent nor more than 49.6 per cent.

METAPHEN.—The anhydride of 4, nitro-5-hydroxymercuri-ortho cresol, $C_2H_2:CH_3ONO_2.Hg$. When metaphen is dissolved in alkali solution, the anhydride ring opens, forming the resulting sodium derivation. Metaphen contains from 56 to 57 per cent of mercury in organic combination.

Actions and Uses.—Metaphen is a germicide, more powerful than mercuric chloride and certain organic mercury compounds when tested on cultures of *Staphylococcus aureus* and *Bacillus typhosus.* It is stated to be relatively nonirritating when applied to mucous membranes or the skin and to be without deleterious action on metallic instruments or rubber. Metaphen is claimed to be relatively nontoxic: white rats were found to tolerate doses of 0.004 Gm. per Kg. when injected intravenously and to tolerate (with but slight pain) doses of 0.03 Gm. per Kg. when injected intramuscularly.

Metaphen is proposed for use in the treatment of gonorrhea and infections of the eye; for skin sterilization and for sterilization of instruments and rubber.

Dosage.—Solutions of metaphen in water are prepared with the aid of sodium hydroxide. For disinfection of instruments solutions of 1 in 5,000 to 1 in 1,000; for application to the skin solutions of 1 in 5,000 to 1 in 1,000; for ophthalmological use solutions of 1 in 10,000 to 1 in 5,000 and for urethral irrigation solutions of 1 in 5,000 to 1 in 10,000 are proposed.

Manufactured by The Abbott Laboratories, North Chicago. U. S. patent 1,554,293 (Sept. 22, 1925; expires 1942). U. S. trademark applied for.

Ampoules Metaphen Solution 1:1,000, 10 Cc.: 1 part metaphen dissolved in 1,000 parts of water by means of sodium hydroxide (four molecules of NaOH for every molecule of metaphen).

Metaphen 2,500: 1 part metaphen dissolved in 2,500 parts of water containing 0.33 per cent each of sodium bicarbonate and sodium carbonate.

Metaphen Solution 1:500: 1 part metaphen dissolved in 500 parts of water by means of sodium hydroxide (four molecules of NaOH for every molecule of metaphen).

Metaphen is a yellow, odorless and tasteless substance; insoluble in water, almost insoluble in methyl alcohol, acetone, ether and aqueous sodium carbonate and sodium bicarbonate solution; soluble in dilute aqueous sodium hydroxide solution and in ammonium hydroxide solution; soluble in boiling glacial acetic acid and in nitric acid at room temperature.

Suspend 0.1 Gm. of metaphen in 10 cc. of glacial acetic acid, allow to stand for five minutes, decant and wash the residue three times by decantation with distilled water; repeat the procedure three times, then dissolve the residue in 15 cc. of distilled water and 1 cc. of 50 per cent sodium hydroxide solution; add 0.5 Gm. of sodium hydrosulphite and heat to boiling: a heavy deposit of metallic mercury is obtained (*combined mercury*). Add 50 cc. of benzene to 0.5 Gm. of metaphen, shake for two minutes, filter, and evaporate the filtrate to dryness: the residue does not weigh more than 0.005 Gm. (*absence of uncombined 4-nitro-2-cresol*). Dissolve 0.4 Gm. of metaphen in 3 cc. of 15 per cent sodium hydroxide solution and 30 cc. of water; divide into two equal portions and transfer to two test tubes; to one add 0.1 Gm. of sodium hydrosulphite, allow to stand for one hour, filter and compare the filtrate with the other tube: the first tube is no darker than the control (*absence of dinitrocresol*). Treat 0.1 Gm. of metaphen with 20 cc. of 1 per cent sodium hydroxide solution: no insoluble residue remains (*absence of inorganic mercury salts or mercury derivative of nitroindazole*).

Transfer about 0.2 Gm. of metaphen, accurately weighed, to a dry Erlenmeyer flask; add 2 Gm. of potassium permanganate, mix well, and then add 5 cc. of diluted sulphuric acid; allow the solution to stand for 15 minutes; then carefully add 15 cc. of sulphuric acid (concentrated) in 2 cc. portions, and allow the mixture to stand for another 10 minutes. Decolorize the mixture drop by drop with hydrogen peroxide solution; after decolorization add 5 cc. of water and boil for from five to eight minutes. Cool, add 150 cc. of water and saturate the solution with hydrogen sulphide; keep the solution saturated for 18 hours. Transfer the precipitated mercuric sulphide to a Gooch crucible; wash with hydrogen sulphide water, then hydrogen sulphide water acidified with sulphuric acid; wash thoroughly with distilled water, then with alcohol and carbon disulphide. The carbon disulphide should remain over the precipitate for approximately one-half hour. Wash finally with acetone. Dry in an oven for one-half hour at 100 to 110 C. and weigh the mercuric sulphide: the amount of mercury calculated from the weight of the mercuric sulphide is not less than 56 per cent, nor more than 57 per cent in the dried substance.

NOVASUROL.—Merbaphen.—The double salt of sodium mercurichlorphenyl oxyacetate with diethylbarbituric acid (barbital).— $NaOOCCH_2.O).Cl.C_6H_3.Hg[CO:\underline{NCO.C(C_2H_5)_2.}$ $\underline{CO}NH]$. Novasurol contains 33.9 per cent of mercury.

Actions and Uses.—Novasurol was introduced originally as an antisyphilitic, but seems to be used chiefly as a diuretic. It has the advantage over mild mercurous chloride and other insoluble mercury compounds in that it is soluble and may be administered by intramuscular or intravenous injection. The best results have been obtained in dropsies due to cardiac disease; it is said to succeed in cases in which the purin derivatives and digitalis have failed. The maximum results are usually obtained when novasurol is employed in conjunction with other diuretic measures, the use of ammonium salts, and the low-fluid, low-salt diet. While contraindicated in nephritis, it has been reported to be useful in nephrosis and glomerulo-nephritis. It is usually ineffective in ascites due to cirrhosis of the liver and Banti's disease, and may be harmful. Some authors, although highly recommending soluble mercury compounds as diuretics, state that they should be used only as a last resort, when other drugs have failed.

As an antisyphilitic, novasurol has generally been injected intravenously mixed with one of the arsphenamines; this is considered by some to be the most satisfactory method of obtaining the combined action of arsenic and mercury. It is recommended, however, that this treatment be followed by the administration of mercury by one of the usual methods.

Dosage.—The dose as a diuretic ranges from 1 to 2 cc. of the 10 per cent solution injected intramuscularly or intravenously. It is recommended that 0.75 cc. be given first, in order to determine the patient's tolerance for mercury. If the drug is well borne, the dose may be increased to 1 cc. or up to 2 cc., according to the effect observed. The drug is given once or twice a week. Digitalis may be given as indicated.

The injections are said to be painless usually, or at least the pain and discomfort are slight and transient; induration at the site of injection is said to be of rare occurrence and of short duration.

The initial dose as an antisyphilitic is 0.75 cc. or 1 cc. of the 10 per cent solution injected intramuscularly once or twice weekly; later the dose may be increased to 2 cc. Recently it has been administered with arsphenamine, 1 cc. of the 10 per cent solution of the drug being mixed with a dose of the arsphenamine and injected intravenously; this was repeated about every five days for eight times.

Manufactured by The Bayer Company, Inc., Rensselaer, N. Y. (Winthrop Chemical Company, New York, distributor). U. S. patent 1,034,092 (July 30, 1912; expires 1929) and 1,074,781 (Oct. 7, 1913; expires 1930). U. S. trademark 106,829.

Novasurol Ampules: Each ampule contains 1.2 cc. of a 10 per cent solution of novasurol and metacresol, 0.05 per cent.

Novasurol occurs as a white crystalline powder, odorless; soluble in cold water. The solution is slightly alkaline. Addition of strong acids to a solution of novasurol yields a precipitate consisting of diethyl barbituric acid, and the mercury derivative of chloro-phenlyoxyacetic acid; on heating the solution the latter breaks up to mercuric chloride and chloro-phenyloxyacetic acid.

To 2 cc. of a solution of novasurol (1 in 1,000) add 0.1 cc. of ferric chloride solution (1 in 25): a flesh colored precipitate forms. Add ammonium sulphide solution to 10 cc. of novasurol 5 per cent: there is developed slowly when cold, and quickly when heated, a black discoloration of the liquid with later formation of a black precipitate of mercuric sulphide. Add 2 cc. of sodium hydroxide solution to 5 cc. of novasurol solution 5 per cent: no precipitate forms. Add 1 cc. of solution of formaldehyde and heat: metallic mercury separates from the solution.

Dry about 1 Gm. of novasurol, accurately weighed, for six hours at 100 C.: the loss in weight is not more than 2 per cent.

Transfer about 0.7 Gm. of novasurol, accurately weighed, to an Erlenmeyer flask; add 100 cc. of water and agitate until powder has dissolved; add 15 cc. of strong hydrochloric acid, connect to a reflux condensor and boil for three hours. Add 175 cc. of hot water, and pass in hydrogen sulphide for fifteen minutes. (It is important that the temperature of the solution should be about 70 C. in order to keep in solution slightly soluble organic compounds formed during hydrolysis.) Filter while warm, through a Gooch crucible, wash with distilled water and finally three portions of cold alcohol and then one portion of carbon disulphide. Close the rubber tubing leading from the suction flask to the suction pump with a pinch clamp; add sufficient carbon disulphide to cover the precipitate, cover the crucible with a watch glass and allow to stand one-half hour. Then release pinch clamp, drain off solution and wash with several portions of carbon disulphide. Dry in an oven at 100 C. for four hours. Weigh the mercuric sulphide and calculate to mercury: the mercury content of the dried specimen is not less than 33 per cent nor more than 34.5 per cent.

Place about 0.5 Gm. of novasurol, accurately weighed, in a tared platinum dish, add 10 cc. of sulphuric acid and gently heat while fumes of sulphur trioxid are evolved. (The mercury is also volatilized.) Cool in desiccator and weigh as sodium sulphate: the sodium calculated from this determination should not be more than 4.0 per cent, nor less than 3.75 per cent.

POTASSIUM MERCURIC IODIDE.—Potassii Hydrargyri Iodidum.—A complex salt, K_2HgI_4, formed by the interaction of one molecule of mercuric iodide with two molecules of potassium iodide and containing about 25.5 per cent of mercury.

Actions and Uses.—Potassium mercuric iodide is used for the same purposes as mercuric iodide, over which it has some advantages because of its solubility. As a germicide it is effective, as it does not coagulate albumin; however, there seems to be no work to show how much the activity is decreased when an excess of potassium iodide is present. In comparison with mercuric chloride it is claimed to have a greater safety factor: Weight for weight, potassium mercuric iodide is about one half as toxic as mercuric chloride according to animal experiments; in proportion to the mercury content, however, potassium mercuric iodide and mercuric chloride possess about the same toxicity.

Externally, potassium mercuric iodide is used for skin disinfection, irrigations, disinfection of instruments, and of excreta and discharges.

Dosage.—As a germicide it is used in concentrations of 1 in 100 to 1 in 10,000. For irrigation of wounds, it is desirable to render the solution isotonic by addition of 0.9 per cent sodium chloride. Solutions of potassium mercuric iodide may be prepared:

(1) By dissolving 1 part by weight of mercuric iodide and 1 part by weight of potassium iodide in a small amount of water and then diluting to proper strength; such a solution will contain about 20 per cent excess of potassium iodide,

sufficient to prevent precipitation of mercuric iodide from dilute solutions of the complex salt. (1 Gm. mercuric iodide is equivalent to 1.7 Gm. potassium mercuric iodide.)

(2) By dissolving potassium mercuric iodide in water containing potassium iodide. Solutions made from potassium mercuric iodide alone have a tendency to decompose with precipitation of mercuric iodide; hence it is necessary to have present an excess of potassium iodide equivalent to about 20 per cent by weight of the amount of potassium mercuric iodide used.

Germicidal Discs of Potassio-Mercuric Iodide No. 1-P. D. & Co.: Disc-shaped tablets of potassium mercuric iodide containing an excess of potassium iodide, colored blue. Each disc represents mercuric iodide, 0.0971 Gm. (1½ grains); potassium iodide, 0.0971 Gm. (1½ grains); sodium bicarbonate, 2.9259 Gm. (45 grains).

Prepared by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

Germicidal Discs of Potassio-Mercuric Iodide No. 2-P. D. & Co.: Disc-shaped tablets of potassium mercuric iodide containing an excess of potassium iodide, colored blue. Each disc represents mercuric iodide, 0.0283 Gm. (⅜ grain); potassium iodide 0.0283 Gm. (⅜ grain); sodium bicarbonate, 1.0368 Gm. (16 grains).

Prepared by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

Kalmerid Germicidal Tablets Potassium Mercuric Iodide: Each tablet contains potassium mercuric Iodide, 0.5 Gm. (7.72 grains); potassium iodide, 0.37 Gm. (5.7 grains); ammonium chloride, 0.125 Gm. (1.83 grains); and eosin "Y," 0.005 Gm. (0.077 grain).

Prepared by Davis & Geck, Inc., Brooklyn, N. Y. U. S. patent 1,276,119 (Aug. 20, 1918; expires 1935). U. S. trademark 116,042.

Sterile Ampoules Mercuric Potassium Iodide, 0.016 Gm. (¼ grain): a solution of potassium mercuric iodide obtained by dissolving red mercuric iodide, 0.01 Gm., and potassium iodide, 0.01 Gm., in water, 1 cc.

Prepared by Swan-Myers Company, Indianapolis.

Potassium mercuric iodide occurs as yellow crystals, deliquescent in air. It is soluble in alcohol and in potassium iodide solution. It yields a clear solution with one part of water. When the solution is diluted with much water, mercuric iodide precipitates slowly; but if one fifth of its weight of potassium iodide is previously added to the salt or its concentrated solution, no mercuric iodide separates on dilution. Its aqueous solution is slightly alkaline to litmus. When the salt is heated in a test tube to the point of fusion, it becomes red, but on cooling again assumes a yellow color; at higher temperatures, there is volatilization of mercuric iodide.

Treat about 0.2 Gm. of potassium mercuric iodide with 1 cc. of water, add 1 cc. of chloroform and 0.5 cc. of ferric chloride solution; the chloroform shows the characteristic color of iodine. Treat about 0.1 Gm. of the salt with 2 cc. of sodium hydroxide solution, and add a few drops of formaldehyde solution; a black precipitate of metallic mercury is produced.

Potassium mercuric iodide loses not more than 4 per cent of its weight when dried at 120 C. for four hours

Transfer about 1.5 Gm. of potassium mercuric iodide, accurately weighed, to a 100 cc. volumetric flask, and dissolve in 1.5 cc. of water, then dilute to 100 cc. Pipette immediately 10 cc. of the solution into a glass stoppered 250 cc. bottle, add 35 cc. of hydrochloric acid and 5 cc. of chloroform. Titrate the solution with tenth normal potassium iodate (10.701 Gm. in 1,000 cc.), stoppering the bottle and shaking the contents well after each addition. The addition of the potassium iodate solution is continued until the iodine which was first liberated disappears, and the chloroform shows no pink color: the iodine content, calculated to the dry salt, is not less than 63.4 per cent nor more than 65.5 per cent.

Dissolve about 2.5 Gm. of potassium mercuric iodide, accurately weighed, in about 10 cc. of water, and add sufficient potassium iodide solution to prevent precipitation of mercuric iodide. Introduce the solution and washings into a cathode cup, previously weighed with its metallic mercury, and add 10 cc. of sodium hydroxide solution, 20 per cent. Pass through the solution an electric current, gradually increasing the current so that at the end of eight minutes it will be 2 to 3 amperes and 7 to 10 volts, stirring the solution by rotating the anode about 500 revolutions per minute. After forty minutes, wash with distilled water, with the aid of a siphon and without interrupting the current until the current drops to zero. Remove the cathode cup and allow it to stand with 20 cc. of acetic acid solution, 3 per cent, until bubbles cease to be evolved. Wash the mercury with water, and then alcohol; remove most of the excess alcohol by filter paper, then dry in a desiccator over potassium hydroxide sticks and a beaker of mercury. The increase in the weight in the cathode cup represents the amount of mercury present in the quantity of the salt taken. The mercury content of potassium mercuric iodide, calculated to the dry salt, is not less than 25.0 per cent, nor more than 26.0 per cent.

Mercury and Potassium Iodide-Merck.—A brand of potassium mercuric-iodide-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.

RED MERCURIC IODIDE.—For description see the U. S. Pharmacopeia and Useful Drugs under Hydrargyri Iodidum Rubrum.

Mercury Biniodide Oil Solution in Ampules, H. W. & D.: One cc. of solution contains red mercuric iodide 0.01 Gm. (1/6 grain) in a neutral, fatty oil. Each ampule contains more than 1 cc.

Prepared by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

Sterile Ampoules Mercury Biniodide 0.01 Gm. (1/6 grain) in Oil: red mercuric iodide-U. S. P., 0.01 Gm., dissolved in purified cottonseed oil, 1 cc.

Prepared by Swan-Myers Company, Indianapolis.

SALYRGAN.—Mersalyl.—Sodium { *o*-[hydroxymercuric-methoxy-propylcarbamyl] phenoxy } acetate.—$NaOOC.CH_2.O.C_6H_4.CONH.C_3H_5(O.CH_3)(HgOH)$. Salyrgan is a complex synthetic mercurial, prepared by the action of mercury acetate and methyl alcohol on salicylallylamido-*o*-acetic acid and subsequent conversion to the sodium salt. Salyrgan when dried to constant weight contains 39.6 per cent of mercury in nonionizable form.

Actions and Uses.—Salyrgan has been demonstrated to exert a destructive action on the spirochete of syphilis in rabbits, but is used chiefly as a diuretic. It induces diuresis only provided sufficient renal tissue is still intact and is therefore contraindicated in acute diseases of the kidney as well as in advanced nephritis. It is effective in ascites and edema of cardiac and cardiorenal origin; also in ascites resulting from cirrhosis of the liver. It has been tried in hydrothorax, pericardial effusion, and in the ascites of tuberculous peritonitis, but without uniform results.

Dosage.—Salyrgan is supplied only in the form of a 10 per cent solution. As diuretic, an initial dose, intramuscularly or intravenously, of 0.5 cc. of the solution to test tolerance, increased to 1 cc. or to a maximum of 2 cc. if required; injections are made at intervals of from three to five days.

Manufactured by H. A. Metz Laboratories, Inc., New York. U. S. patent 1,693,432 (Nov. 27, 1928; expires 1945). U. S. trademark 188,515.

Ampules Salyrgan Solution, 1 cc.: Each ampule contains 1 cc. of a 10 per cent solution of salyrgan.

Salyrgan occurs as a white, crystalline, odorless powder with a bitter taste; readily soluble in ethyl alcohol, about 1 in 3, methyl alcohol, about 1 in 2 and water, about 1 in 1, and insoluble in ether. An aqueous solution is alkaline to litmus paper.

Dissolve 0.5 Gm. in 5 cc. of water, add 5 cc. of formic acid (90 per cent), boil the mixture under a reflux condenser for fifteen minutes: the precipitate formed dissolves, leaving a gray residue containing fine globules of metallic mercury. Filter the mixture through paper while hot; allow the filtrate to cool, collect the resultant salicylallylamido-*o*-acetic acid crystals on a filter paper, wash and dry over sulphuric acid in a partially exhausted desiccator: it melts at 120-121 C. Dissolve about 1 Gm. in 10 cc. of water, add 10 cc. of a solution of hydrochloric acid (1 part hydrochloric acid and 1 part water), connect to a condenser, distil off about three fourths the volume: the distillate responds to tests for methyl alcohol. Dissolve 0.5 Gm. in 5 cc. of water, add 0.5 cc. of diluted acetic acid and 0.3 cc. of sodium sulphide solution: no coloration results (*heavy metals—especially mercuric ions*). Dissolve 0.1 Gm. in 5 cc. of water, add 1 cc. of nitric acid, filter through paper and divide the filtrate into two portions; to one portion add 1 cc. of silver nitrate solution: no opalescence results (*chlorides*); to the other portion add 1 cc. of barium nitrate solution: no turbidity results (*sulphates*). Dissolve 0.5 Gm. in 10 cc. of water, add 1 cc. diluted sulphuric acid, filter through paper and divide the filtrate into two portions; to one portion add 0.1 cc. of tenth-normal potassium permanganate solution: no immediate decolorization results (*salicylallylamido acetic acid*); to the remaining portion add 0.1 cc. of diluted ferric chloride solution; no violet color develops (*salicyllylamide*). When tested for arsenic according to the U. S. Pharmacopeia X, the product meets the requirements for arsenic (p. 428, Arsenic Test).

Dry about 1 Gm., accurately weighed to constant weight over sulphuric acid in a partially exhausted desiccator: the loss in weight does not exceed 5.0 per cent. Transfer about 0.5 Gm., accurately weighed, to a 500 cc. Kjeldahl flask, and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, Second Edition, p. 8. The percentage of nitrogen corresponds to not less than 2.55 per cent, nor more than 3.0 per cent when calculated to the dried substance. Weigh accurately about 0.5 Gm. in a tared platinum dish, add 10 cc. of sulphuric acid, gently heat while fumes of sulphur trioxide are evolved, repeat, using two portions of 2 cc. of sulphuric acid, respectively, ignite, cool and weigh as sodium sulphate. The percentage of sodium corresponds to not less than 4.3 per cent, nor more than 4.9 per cent, when calculated to the dried substance. Transfer about 0.5 Gm., accurately weighed, to an Erlenmeyer flask; add 100 cc. of water and agitate until the powder has dissolved; add 15 cc. hydrochloric acid, connect to a reflux condenser and boil for three hours. Add 175 cc. of hot water, and pass in hydrogen sulphide for fifteen minutes. (It is important that the temperature of the solution should be about 70 C. in order to keep in solution slightly soluble organic compounds formed during hydrolysis.) Filter while warm, through a Gooch crucible, wash with distilled water and finally three parts of cold alcohol and then one portion of carbon disulphide. Close the rubber tubing leading from the suction flask to the suction pump with a pinch clamp; add sufficient carbon disulphide to cover the precipitate, cover the crucible with a watch glass and allow to stand one-half hour. Then release the pinch clamp, drain off the solution and wash with several portions of carbon disulphide. Dry in an oven at 100 C., weigh the mercury sulphide and calculate to mercury. The percentage of mercury corresponds to not less than 38.0 per cent, nor more than 41.0 per cent, when calculated to the dried substance.

YELLOW MERCURIC OXIDE.—For description see U. S. Pharmacopeia and Useful Drugs under Hydrargyri Oxidum Flavum.

Compound Yellow Oxide and Adrenalin Ointment-M. E. S. Co.: Yellow oxide of mercury, 1 per cent; solution of adrenalin chloride 5 per cent; menthol 0.04 per cent; phenol 0.2 per cent; hydrous wool fat 25 per cent, and white petrolatum sufficient to make 100 per cent. Put up in collapsible tubes, for application to the eye.

Prepared by Manhattan Eye Salve Co., Louisville, Ky. No U. S. patent or trademark.

Mercurous Compounds

CALOMELOL.—Hydrargyri Chloridum Mite Colloidale.—Colloidal Calomel.—A colloidal form of calomel, containing albuminoids.

Actions and Uses.—The action of calomelol is the same as that of calomel, but it is claimed that it is superior because of its power of forming colloidal suspension in water, acting more rapidly and efficiently, and that it is nonirritant. The indications for its use are the same as for calomel.

Dosage.—Internally, the same as calomel. Externally it is used as a dusting powder, mixed with an equal quantity of starch or of a mixture of starch and zinc oxide, or in the form of calomel ointment. It should be protected from the light.

Manufactured by Heyden Chemical Corporation, New York. U. S. patent 740,855 (Oct. 6, 1902; expired). U. S. trademark.

Calomelol Ointment: Twenty-eight per cent mercury in the soluble form of calomelol (which see) and 2 per cent in the insoluble form.

It is prepared by combining 45 parts of calomelol with sufficient lard to make 100 parts.

Dosage.—6 Gm. (90 grains) daily for inunction in syphilis.

According to the patent, calomelol is prepared by acting on a solution of sodium chloride in the presence of a protein with mercurous nitrate and precipitating the colloidal calomel by means of alcohol. The precipitate is washed with alcohol, redissolved in water with the aid of a little alkali, and from this solution the colloidal calomel is obtained, either by evaporation or by precipitation with alcohol.

It forms a white-gray, odorless and tasteless powder, containing 80 per cent of mercurous chloride and 20 per cent of protein. With water, it forms an opalescent suspension insoluble in alcohol, ether and benzene. (In these suspensions, colloidal bodies are in such an extreme state of subdivision that they were formerly supposed to be in solution and are still so considered.) It is precipitated from its aqueous suspension by acids, the precipitate being redissolved by alkalis.

Mercury (Metallic) Preparations

MERCURIAL OINTMENT, IMPROVED-MULFORD.—An ointment containing 50 per cent of metallic mercury in an ointment base consisting of wool fat, petrolatum and suet, aromatized.

Actions and Uses.—The same as those of mercurial ointment-U. S. P. Mercurial ointment, improved, is devoid of the unpleasant odor of mercurial ointment-U. S. P., and is claimed to be more readily absorbed.

Dosage.—The same as that of mercurial ointment-U. S. P.

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

Capsules Mercurial Ointment, Improved-Mulford, 30 grains.

Capsules Mercurial Ointment, Improved-Mulford, 60 grains.

Mercurial ointment, improved, is a slate-colored, semisolid mass, having a pleasant, aromatic odor.

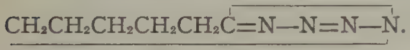
MERCURETTES-P. D. & CO.—Tabellae Hydrargyri Cum Oleo Theobromatis.—Briquettes, each containing finely divided metallic mercury 3.25 Gm. (50 grains) incorporated with theobroma (cacao butter) and perfumed. Each briquette weighs 8 Gm. (120 grains).

Actions and Uses.—The same as those of ointment of mercury-U. S. P. It is claimed that in the treatment of syphilis and certain forms of parasitic skin diseases where ointment of mercury has been employed, the use of mercurettes permits a more accurate dosage and is more convenient and less disagreeable.

Dosage.—Applied by inunction. If less than one briquette is to be used, it may be divided by cutting with a knife.

Prepared by Parke, Davis & Co., Detroit. No U. S. patent. U. S. trademark 180,215.

METRAZOL.—Pentamethylenetetrazol.—



$CH_2CH_2CH_2CH_2CH_2C{=}N{-}N{=}N{-}N$.

Actions and Uses.—The action of metrazol is similar to that of camphor, but it is claimed to be more dependable, mainly on account of its greater solubility in water. Its action following injection intravenously or subcutaneously is induced promptly. Metrazol stimulates the vasomotor and respiratory centers in experiments on normal animals, but an experienced worker in this field found it a very uncertain respiratory stimulant in conditions of depressed respiration in animals, in which carbon dioxide, epinephrine and ephedrine were markedly effective; that as a circulatory stimulant it usually caused a rise of blood pressure only in convulsive doses; that it did make irregularly beating hearts beat more regularly, but only at expense of depression of rate and amplitude. The use of metrazol is reported as a sustaining agent and restorative in chronic cardiac and circulatory insufficiency, in pneumonia, and in other infectious diseases. It has been reported to be of value in the emergency of cardiovascular collapse, in shock, in respiratory failure, and in narcotic depression. On the other hand, it causes capillary dilatation in the splanchnic region, and animal experiments indicate that the intravenous injection may be distinctly dangerous. It may be combined with digitalis and the xanthine diuretics.

Dosage.—Intramuscularly or intravenously, 0.1 Gm. (1½ grains) every one to three hours; orally, from 0.1 to 0.2 Gm. (1½ to 3 grains) several times daily as required.

Manufactured by Knoll A.-G., Ludwigshafen a. Rh., Germany (E. Bilhuber, Inc., New York, distributor). U. S. patent 1,599,493 (Sept. 14, 1926; expires, 1943). U. S. trademark 249,687.

Metrazol Ampules, 1 cc.: Each ampule contains 1.1 cc. of a 10 per cent aqueous solution of metrazol.

Metrazol Tablets: Each tablet contains 1½ grains of metrazol.

Metrazol occurs as biaxial, optically negative, white crystals that are freely soluble in water. It melts at 57-58 C.

To a 10 per cent aqueous solution of metrazol add a saturated solution of mercuric chloride: a white solid precipitate results, which may be recrystallized from hot water or alcohol to yield crystals melting at 177-178 C. and leaving not more than 0.1 per cent of ash on incineration.

Transfer about 0.2 Gm. of metrazol, accurately weighed, to a wide mouth weighing bottle; allow to stand over calcium chloride: the loss in weight is not more than 0.1 per cent.

Transfer about 0.2 Gm. of metrazol, accurately weighed, to a platinum dish and incinerate: the ash is not weighable.

Determine nitrogen by the Dumas method as described in Clarke's Handbook of Organic Analysis, ed. 2, p. 199: the nitrogen is not less than 40.4 nor more than 40.9 per cent.

NAPHTHOL COMPOUNDS

Compounds of naphthol that are insoluble in the stomach have been introduced in therapeutics. The expectation was that, owing to the greater concentration of the naphthol in the intestines after its liberation by the bile and pancreatic juices, these compounds would have a maximum antiseptic action. In addition, the action of whatever substance was united with the naphthol would be exerted, whether on the intestine or on some other part of the body, such as the genito-urinary tract.

A wide difference of opinion, however, exists among authorities as to the actual efficacy of all intestinal antiseptics and of most urinary antiseptics. Whatever opinion regarding this is held, it should be remembered that any of them, if used freely or for a long time, may have irritating effects on the digestive tract or undesirable effects on other tissues. Reasonable caution should therefore be exercised in using them.

BETANAPHTHYL BENZOATE.—Betanaphtholis Benzoas.—Betanaphthol Benzoate.—Benzonaphthol.—$C_6H_5COO.(C_{10}H_7)$.—The benzoic acid ester of betanaphthol.

Actions and Uses.—Betanaphthyl benzoate is not decomposed by the gastric fluid, but is split into its constituents in the intestinal canal.

Betanaphthyl benzoate is used internally as an intestinal antiseptic in diarrhea and typhoid fever. Externally, betanaphthyl benzoate is used as a parasiticide in the form of from a 3 to a 10 per cent ointment. It has been used in psoriasis, eczema, scabies, etc.

Dosage.—From 0.2 to 0.5 Gm. (3 to 8 grains); maximum dose, single, 1 Gm. (15 grains), daily 4 Gm. (60 grains).

Betanaphthyl benzoate occurs in colorless needles, or as a white, tasteless, crystalline powder of faintly aromatic odor. It darkens with age. It is almost insoluble in water, very soluble in alcohol and ether, and soluble in chloroform and fixed oils. It melts at from 107 to 110 C.

Betanaphthyl benzoate heated with a solution of potassium hydroxide in alcohol develops the odor of ethyl benzoate; on the addition of chloroform the mixture acquires a blue color. Shake vigorously for one minute 1 Gm. of betanaphthyl benzoate with 20 cc. of a cold 5 per cent aqueous sodium hydroxide solution, and filter immediately. To 10 cc. of the filtrate, add 2 cc. of chloroform, and boil: no blue color is produced in the aqueous layer (*uncombined betanaphthol*). Carefully neutralize the remaining 10 cc. of the alkaline filtrate, then add a few drops of ferric chloride solution previously diluted with two volumes of water and neutralize, if necessary, with ammonia water: no pink precipitate is produced (*uncombined benzoic acid*). Shake vigorously for one minute 0.5 Gm. of betanaphthyl benzoate with 5 cc. of an aqueous 5 per cent sodium hydroxide solution and filter: no blue color develops in the filtrate on the addition of a few drops of iodine solution (*alphanaphthol*).

Shake vigorously for one minute 0.5 Gm. of betanaphthyl benzoate with 50 cc. of distilled water and filter: the filtrate should not be acid toward litmus. Five cc. portions of the filtrate mixed with equal volumes of diluted nitric acid do not become turbid on the addition of 1 cc. of silver nitrate solution (*chloride*) or of barium nitrate solution (*sulphate*).

Incinerate 0.5 Gm. of betanaphthyl benzoate: not more than 0.1 per cent of ash remains.

Betanaphthol Benzoate-Merck.—A brand of betanaphthyl benzoate-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributors. No U. S. patent or trademark.

Betanaphthol Benzoate-Seydel.—A brand of betanaphthyl-N. N. R.

Manufactured by The Seydel Chemical Company, Jersey City, N. J.

BETANAPHTHYL SALICYLATE.—Betanaphtholis Salicylas.—$C_6H_4.OH.COO(C_{10}H_7)$.—The salicylic acid ester of betanaphthol.

Actions and Uses.—Betanaphthyl salicylate undergoes no change in the stomach, but is split up into its original compounds, when it reaches the intestinal tract, by the pancreatic juice and intestinal secretions. It is believed to act as an intestinal antiseptic and, being excreted in the urine, to act in a similar way in the bladder. (See preceding article, Naphthol Compounds.)

It has the antirheumatic properties of salicylic acid. It is said to be useful in intestinal fermentations, catarrh of the bladder, particularly gonorrheal cystitis, rheumatism, etc.

Dosage.—From 0.3 to 0.5 Gm. (4 to 8 grains) in cachets, milk or emulsion.

It is a white lustrous crystalline powder, colorless and tasteless, melting between 93 and 95 C. It is insoluble in cold or hot water or glycerin, soluble with difficulty in cold alcohol or turpentine, easily soluble in boiling alcohol, in ether, in benzene, and in raw linseed oil. In the cold it is not changed by acids or alkalis of moderate concentration. When heated with alkalis it is decomposed into its constituents, which, if the solution be acidulated, will crystallize.

It is distinguished from salol by its higher melting point and by the production of a brownish-green color, when a trace of nitric acid is added to its yellow colored solution in pure sulphuric acid. It burns on platinum foil, leaving no residue (*fixed mineral impurities*). If 1 Gm. of betanaphthyl salicylate is shaken with 30 Gm. of boiling water and filtered through a moistened filter, the filtrate should not have an acid reaction (*salicylic, hydrochloric or phosphoric acid*); it should not, after cooling, show a crystalline deposit (*salicylic acid or betanaphthol*); it should not become turbid on the addition of silver nitrate (*chlorides or phosphates*) or barium nitrate (*sulphate*), nor should it give a violet color with solution of ferric chloride.

BISMUTH BETANAPHTHOL.—See Bismuth Compounds.

NEOROBIN.—A product obtained by the reduction of chrysarobin.

Actions and Uses.—The same as those of chrysarobin. It is claimed that neorobin is somewhat more active than chrysarobin and that it has the advantage over chrysarobin in that its staining qualities are markedly less.

Like chrysarobin, neorobin is used in skin diseases, especially psoriasis. It is claimed to be of value in the treatment of pityriasis capitis (dandruff) and in low grade inflammations of the skin, and in conditions in which a cutaneous stimulant and roborant is indicated.

Dosage.—It is applied in the form of ointments made with petrolatum, containing from 0.2 to 1 per cent (1 to 5 grains per ounce). Ointments must be freshly made, dispensed in collapsible tubes and used within two weeks from the time of preparation.

Manufactured by the H. K. Mulford Co., Philadelphia, under U. S. patent 1,417,771 (May 30, 1922; expires 1939) issued to J. F. Schamberg and G. W. Raiziss. No U. S. trademark.

Vacuum Sealed Tubes Neorobin, 1 grain.

Vacuum Sealed Tubes Neorobin, 5 grains.

Neorobin is prepared by dissolving chrysarobin in glacial acetic acid and subsequent reduction with metallic tin in the presence of hydrochloric acid. The hot liquid is treated with charcoal and filtered; on cooling, the crystals of neorobin separate out. The precipitate is washed with water, ethyl alcohol and ether.

Neorobin is a yellow or yellowish gray powder, slightly soluble in ether and methyl alcohol; more soluble in glacial acetic acid, chloroform, benzene and ethyl alcohol; readily soluble in acetone. Neorobin readily oxidizes when exposed to the air; also when in contact with fats.

When dissolved in acetone, neorobin yields a golden yellow solution (*distinction from chrysarobin, which yields a dark red solution*).

Incinerate neorobin, 0.5 Gm.: the ash is not more than 0.7 per cent. Treat 0.1 Gm. of neorobin according to the test of Masucci and Slothower (*J. Am. Pharm. A.* **12**: 337): not less than 0.11 Gm. of metallic silver is found.

NITRATES—ORGANIC

The esters of nitric acid and the higher alcohols (glycerin, propanetriol, erythrite (butanetetrol), etc., have an action on the blood vessels similar to that of the inorganic nitrites (sodium nitrite) and that of the nitrous acid esters of the alcohols (amyl nitrite, ethyl nitrite). This is generally attributed to the formation in the body, of nitrites from them. The action of organic nitrates differs from that of the organic nitrites chiefly in that the action of the former is longer continued. This is seen in the case of glyceryl trinitrate, U. S. P. (nitroglycerin), and, to a still greater degree, in the following:

ERYTHROL TETRANITRATE.—Tetranitrol.—$C_4H_6(NO_3)_4$.—The tetranitrate of erythrite (butanetetrol), $C_4H_6(OH)_4$.

Actions and Uses.—Erythrol tetranitrate is a vasodilator like nitroglycerin. Its action is slower and more lasting, beginning in fifteen minutes and persisting for three or four hours.

It is said to be useful in angina pectoris and vascular diseases. It is reported as especially useful as a prophylactic in preventing anginal pain.

Dosage.—From 0.03 to 0.06 Gm. (½ to 1 grain) every four to six hours. Like nitroglycerin and many similar organic nitrates, it is a violent explosive. Sold in the form of tablets only.

Merck & Co., Inc., Rahway, N. J., distributor. German patent 81,664.

Erythrol Tetranitrate Tablets-Merck, ½ grain.

Erythrol Tetranitrate Tablets-Merck, ¼ grain.

Erythrol tetranitrate is obtained by the nitration of the tetratomic alcohol erythrite.

It forms colorless crystalline scales, insoluble in cold water, but readily soluble in alcohol, and melting at 61 C. On percussion it explodes, much like nitroglycerin.

OPIUM PRINCIPLES, DERIVATIVES AND PREPARATIONS

Morphine is a complex derivative of phenanthrene. It contains two OH groups (one phenolic, the other alcoholic) in which substitutions can be made by either alkyl or acid radicals.

The more important alkyl esters are the monomethyl (codeine); the dimethyl (thebaine); and ethyl-morphine. Heroin is the diacetyl derivative.

The nature of these radicals—whether acid or alcoholic, aromatic or aliphatic—modifies the actions, quantitatively, but only in a degree. Replacement of one hydroxyl group (codeine) diminishes the narcotic action and increases the respiratory and tetanic action. When both OH groups are replaced by acids (diacetyl morphine), the narcotic effects are stronger than with codeine, and the tetanic action is weaker than with morphine.

Actions and Uses.—The central actions of all these morphine derivatives are qualitatively identical; but they present quantitative differences which have some practical importance:

Morphine produces the strongest narcotic, analgesic, hypnotic and intestinal effects, and the weakest stimulation. It causes the greatest derangement of digestion. It and diacetyl morphine are most liable to induce a habit.

Codeine (methyl-morphine) is less narcotic, less constipating, and less apt to induce tolerance and habit. It is, therefore, especially valuable in cough or in other conditions in which the sedative action must be continued for some time and in patients who do not tolerate morphine. (See also Codeine Derivatives.)

Ethyl-Morphine seems to stand intermediate between morphine and codeine, in all respects. The hydrochloride is used as a sedative, but mainly for its special action on the conjunctiva, as described below.

Diacetyl-Morphine (heroin) closely approaches morphine, of which it shares all the disadvantages, and over which it has no important advantage. It was originally introduced with the claim that therapeutic doses lessen the cough reflex and slow the respiration, but that the inspirations are deepened and more powerful, so that the alveolar air is more effectively ventilated. Independent workers, however, have shown that there is no real difference from morphine in these respects. It is now generally conceded that diacetyl-morphine is as effective as morphine in cough, but not more so; that it is rather less effective against dyspnea; and that it is more liable to produce habit and toxic effects. Codeine seems to be superior to diacetyl morphine in its power to allay cough, to overcome pain and to promote sleep (Bastedo).

PANTOPON-ROCHE. — Pantopium Hydrochloricum. — A mixture of the hydrochlorides of the alkaloids of opium in the proportion in which they exist in Smyrna opium, containing 50 per cent of anhydrous morphine hydrochloride.

Actions and Uses.—Pantopon-Roche (pantopium hydrochloricum) produces essentially the effects of opium, but, being devoid of its extractive, it may be used for hypodermic administration. It is probably absorbed rather more promptly, and is free from the nauseant odor and taste of the ordinary opium preparations. It is used in the same conditions as those in which opium is indicated.

Dosage.—For adults, 0.005 to 0.02 Gm. ($\frac{1}{12}$ to $\frac{1}{3}$ grain) hypodermically or by mouth. One grain of pantopon-Roche (pantopium hydrochloricum) is equivalent to:

2.5 grains of extract of opium-U. S. P.
4.5 grains of powdered opium-U. S. P.
45.0 minims of tincture of opium-U. S. P.
0.6 grain of morphine sulphate-U. S. P.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J.). U. S. patent 1,056,219 (March 18, 1913; expires 1930). **U. S. trademark 77,371.**

Pantopon-Roche (Pantopium Hydrochloricum) Tablets: Pantopon-Roche (pantopium hydrochloricum) 0.01 Gm.

Pantopon-Roche (Pantopium Hydrochloricum) Hypodermic Tablets: Pantopon-Roche (pantopium hydrochloricum) 0.02 Gm.

Pantopon-Roche (Pantopium Hydrochloricum) Ampules for Hypodermic Administration: One cubic centimeter of solution contains 0.02 Gm. of pantopon-Roche (pantopium hydrochloricum). Each ampule contains 1.1 cc. of sterile solution.

Pantopon-Roche (pantopium hydrochloricum) is a yellowish-gray crystalline powder which is readily soluble in water.

If a few drops of ammonia water are added to an aqueous solution of pantopon-Roche (pantopium hydrochloricum) (1 in 200) a precipitate of the secondary opium alkaloids forms at once (*distinction from pure morphine hydrochloride*).

If from 0.5 to 1 Gm. of pantopon-Roche (pantopium hydrochloricum) is weighed and dried at 100 C. to constant weight, the loss should correspond to from 9 to 9.5 per cent of the weight taken.

If from 0.5 to 1 Gm. of pantopon-Roche (pantopium hydrochloricum) is weighed and dissolved in water containing a little nitric acid, and the hydrochloric acid is determined by precipitation with silver nitrate and by weighing the precipitate in the usual way, the silver chloride found corresponds to between 9.8 per cent and 10.2 per cent of hydrochloric acid (HCl).

If 0.8 Gm. of pantopon-Roche (pantopium hydrochloricum) is dissolved in sufficient water to make 40 Gm. of solution, 2 Gm. of normal ammonia water added, the solutions mixed by circulatory rotation (not by shaking), and the solution immediately filtered through a dry filter, and if 36.75 Gm. of the filtrate, equivalent to 0.7 Gm. of pantopon-Roche (pantopium hydrochloricum) is treated with 10 cc. of ether and 4 cc. of normal ammonia water, and the assay process completed as described in the Swiss Pharmacopeia, ed. 4, p. 344, for opium, the tenth-normal hydrochloric acid consumed corresponds to from 44 to 45 per cent of anhydrous morphine.

PAPAVERINE. — Papaverina. — $C_{20}H_{21}O_4N$. — An alkaloid obtained from opium, belonging to the benzyl isoquinoline group (that is, it is not a morphine derivative).

Actions and Uses.—Pal found that papaverine relaxes smooth muscle in general, although different organs are affected in a varying degree.

Papaverine is most effective in hypertonic conditions, while it does not interfere materially with the normal movements, for instance, of the intestines. It is also a rather feeble central analgesic and a local anesthetic. Its toxicity is low, and neither tolerance nor habituation has been reported. These actions have prompted its use, with reported success, in various spasmodic conditions of the smooth muscles. Pal recommends it especially in all kinds of gastric and intestinal spasms (also for the diagnosis of pyloric spasm), in biliary colic, and in bronchial spasm. Of more doubtful value is its employment in pertussis, hyperemesis, and vascular spasm—angina pectoris, acute uremia and eclampsia. It is admitted to be ineffective in chronic hypertonus. The local anesthetic action, with vasodilatation, has been used against rhino-asthma, and to mitigate the pain of irritant injections.

Dosage.—The oral and hypodermic single dose is from 0.03 to 0.08 Gm. (½ to 1⅓ grain); daily dose to 0.5 Gm. (7½ grains). Single doses of even 1 Gm. (15 grains) are said to be nontoxic.

Papaverine occurs in fine, white rhombic prisms or needles or sometimes in scales; it is odorless and tasteless. It is nearly insoluble in cold water; slightly soluble in alcohol, ether, chloroform and benzene if cold; somewhat more soluble in these liquids when hot, but deposited by them on cooling, and soluble in warm petroleum ether and in acetone. It melts at 147 C.

If about 0.01 Gm. of papaverine is dissolved in 10 cc. of water containing a few drops of diluted hydrochloric acid, and a few drops of potassium ferricyanide solution is added, a lemon yellow precipitate of papaverine ferricyanide should form at once (*distinction from other opium alkaloids*). If about 0.001 Gm. of papaverine is dissolved in 0.1 cc. of sulphuric acid containing in each cubic centimeter 1 drop of formeldehyde solution, a colorless or, at most, a faintly yellowish-green solution should be produced. This gradually changes to deep rose and finally becomes brown (*distinction from morphine and its esters,* which give purple or violet colors). If 0.01 Gm. of papaverine is dissolved in 0.2 cc. of sulphuric acid, the solution should not be colored more deeply than a very faint pink or brown (limit of *cryptopine, thebaine or of other organic impurities*). If 0.01 Gm. of papaverine is dissolved in 10 cc. of water containing a few drops of hydrochloric acid, a few drops of a saturated aqueous solution of iodic acid added, and the mixture shaken with chloroform, the chloroform layer should not be colored violet (*morphine*).

If from 0.2 to 0.3 Gm. of papaverine is weighed, dissolved in 20 cc. of warm water containing a few drops of diluted hydrochloric acid, the solution cooled, 1 cc. of freshly prepared potassium ferricyanide solution added, the mixture agitated, allowed to stand over night and filtered, the filtrate made alkaline with ammonia water, shaken with several successive portions of ether, the ether solutions combined, washed with water, evaporated, the residue dried at 100 C. and weighed, the weight should not amount to more than 2 per cent of the weight taken (limit of *foreign opium alkaloids*).

PAPAVERINE HYDROCHLORIDE.—Papaverinae Hydrochloridum.—$C_{20}H_{21}O_4N.HCl$.—The hydrochloride of the alkaloid papaverine, containing not less than 88 per cent of papaverine.

Actions, Uses and Dosage.—See Papaverine.

Papaverine hydrochloride occurs in a fine white, crystalline powder or in small monoclinic plates or prisms; odorless and having a bitter taste; permanent in the air. It is sparingly soluble in water; soluble in alcohol; very soluble in chloroform, and insoluble in ether. An aqueous solution of papaverine hydrochloride has an acid reaction toward litmus paper.

If from 0.2 to 0.3 Gm. of papaverine hydrochloride is weighed, dissolved in 20 cc. of warm water, the solution cooled, a slight excess of ammonia water added and the mixture shaken with three successive portions of 25 cc. each of ether, or a sufficient quantity to complete the extraction, the ether solutions combined, washed with water, evaporated to dryness, the residue dried to constant weight at 100 C. and weighed, the weight should indicate not less than 88 per cent of papaverine. The alkaloid obtained by this process should conform to the tests for identity and purity described under Papaverine.

Papaverine Hydrochloride-Merck.—A brand of papaverine hydrochloride-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.

Papaverine Hydrochloride-Roche.—A brand of papaverine hydrochloride-N. N. R.

Manufactured by Hoffmann-LaRoche, Inc., Nutley, N. J.

PAPAVERINE SULPHATE.—Papaverinae Sulphas.—$(C_{20}H_{21}O_4N)_2H_2SO_4$.—The sulphate of the alkaloid papaverine, containing not less than 85 per cent of papaverine.

Actions, Uses and Dosage.—See Papaverine.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J.).

Papaverine Sulphate-Roche, Ampules.—One cc. of solution contains papaverine sulphate, 0.04 Gm. Each ampule contains 1.1 cc. of solution.

Papaverine Sulphate Tablets-Roche, 0.04 Gm.

Papaverine sulphate occurs in white, crystalline powder; odorless and having a bitter taste; slightly hygroscopic. It is soluble in water and in alcohol; very soluble in chloroform; insoluble in ether. An aqueous solution of papaverine sulphate has an acid reaction to litmus paper.

If from 0.2 to 0.3 Gm. of papaverine sulphate is weighed, dissolved in 20 cc. of water, a slight excess of ammonia water added and the mixture shaken with three successive portions of 25 cc. each of ether, or a sufficient quantity to complete the extraction, the ether solutions combined, washed with water, evaporated to dryness, the residue dried to constant weight at 100 C. and weighed, the weight should indicate not less than 85 per cent of papaverine. The alkaloid obtained by this process should conform to the tests for identity and purity described under Papaverine.

ORGANS OF ANIMALS

The discovery of the importance of internal secretions has led to extensive clinical trials with preparations of the so-called ductless glands, and other tissues which elaborate, or are supposed to elaborate, such internal secretions. Four of these, the thyroid and suprarenal glands, the posterior lobe of the pituitary and insulin obtained from the pancreas have given decisive therapeutic results. Thyroid in the form of the desiccated gland, epinephrine, an active principle of the suprarenal glands, and solution of pituitary prepared from the posterior lobe of the pituitary, are included in the U. S. Pharmacopeia; insulin is described in this book. The other organ products are scarcely beyond the experimental stage. Their active principles (with the possible exception of the estrus-producing principle found in the ovary) have not been isolated, and they are most commonly used in the form of the powdered dried gland. The gross fat and connective tissue is removed as completely as possible, and the drying is conducted at a relatively low temperature. The powder (often improperly called an "extract") is frequently compressed into tablets. The Council recommends that the strength of these be stated in terms of the dried gland. Since, in general, there are no tests for the quality, or even identity, of these powdered products, the physician, unless he can himself supervise their preparation, is forced to rely on the general reputation of the manufacturer.

After the description of each gland, a list of such preparations as have been submitted to the Council, and are being maketed in an acceptable manner, is given. For the reasons stated, however, the Council disclaims any responsibility for their quality or identity.

OVARY

The ovaries produce internal secretions which are necessary for the proper functioning of the uterus and which also have obscure effects on metabolism and on the nervous system. It is believed that ovarian function is maintained by hormone action. While the action of some of the ovarian hormones appears to be exclusively on the organs of the genital tract or on the ovary itself, other hormones appear to have perhaps indirectly a more general influence (basal metabolism, bone-growth, nervous system).

Various preparations of the ovary of animals have been used in the treatment of conditions believed to be due to ovarian dysfunction, on the assumption that the preparations contain the active principles or hormones of the ovary. Preparations of the whole ovary, corpus luteum, liquor folliculi and ovarian residue have been employed.

Rational as ovarian therapy may theoretically appear to be in some conditions, the actual results are rarely striking, and often nil to the careful observer. It is altogether probable that the activity which may be presented by the fresh gland is not contained in a finished desiccated product, or else, when given by mouth, it is destroyed by the digestive juices; extensive clinical experience has failed to establish the value of desiccated preparations administered orally. There is considerable evidence that the aqueous extracts prepared for hypodermic use are inert; favorable reports have often concerned cases in which ovarian products were given together with preparations of the thyroid gland, the activity of which is not destroyed in the digestive tract. Much work has been done toward the elaboration of a potent, standardized preparation of the ovary, and as a result of these investigations such potent standardized preparations for use by subcutaneous injection have become available. These preparations have been shown to induce estrus in mature animals and to induce sexual maturity in immature animals. Somewhat limited clinical evidence indicates their probable value in ovarian hypofunction.

OVARIAN SUBSTANCE SOLUBLE EXTRACT-P. D. & CO.—A solution of an extract of desiccated beef and hog ovaries in physiological solution of sodium chloride, each cubic centimeter containing 0.04 Gm. of soluble extract, preserved by the addition of 0.5 per cent of chlorbutanol.

Actions and Uses.—See preceding article, Ovary.

Dosage.—One cc. at intervals of one to two days.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

Ampoules Ovarian Substance Soluble Extract-P. D. & Co., 1 cc.

Ovarian substance soluble extract-P. D. & Co. is made by extracting desiccated ovarian substance with water slightly acidulated with acetic acid, containing 0.5 per cent of chlorbutanol. The extract is filtered, concentrated in a vacuum at low temperature and precipitated by a solvent miscible with the solution, such as alcohol or acetone. The precipitate is collected, dried at a low temperature and dissolved in physiological solution of sodium chloride so that each cubic centimeter contains 0.04 Gm.

OVARIAN RESIDUE SOLUBLE EXTRACT-P. D. & CO.—A solution of an extract of desiccated beef and hog ovaries, from which the corpora lutea have been removed, in physiological solution of sodium chloride, each cubic centimeter containing 0.04 Gm. of soluble extract, preserved by the addition of 0.5 per cent of chlorbutanol.

Actions and Uses.—See preceding article, Ovary.

Dosage.—One cc. at intervals of one to two days.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

Ampoules Ovarian Residue Soluble Extract-P. D. & Co., 1 cc.

Ovarian residue soluble extract-P. D. & Co. is made by extracting desiccated ovarian substance, from which the corpora lutea have been removed, with water slightly acidulated with acetic acid, containing 0.5 per cent of chlorbutanol. The extract is filtered, concentrated in a vacuum at low temperature and precipitated by a solvent miscible with the solution, such as alcohol or acetone. The precipitate is collected, dried at a low temperature and dissolved in physiological solution of sodium chloride, so that each cubic centimeter contains 0.04 Gm.

CORPORA LUTEA SOLUBLE EXTRACT-P. D. & CO.—A solution of an extract of desiccated corpus luteum in physiological solution of sodium chloride, each cubic centimeter containing 0.02 Gm. of soluble extract, preserved by the addition of 0.5 per cent of chlorbutanol.

Actions and Uses.—See preceding article, Ovary.

Dosage.—One cc. at intervals of one to four days.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

Ampoules Corpora Lutea Soluble Extract-P. D. & Co., 1 cc.

Corpora lutea soluble extract-P. D. & Co. is made by extracting desiccated corpus luteum with water slightly acidulated with acetic acid, containing 0.5 per cent of chlorbutanol. The extract is filtered, concentrated in a vacuum at low temperature and precipitated by a solvent miscible with the solution, such as alcohol or acetone. The precipitate is collected, dried at a low temperature and dissolved in physiological solution of sodium chloride so that each cubic centimeter contains 0.02 Gm.

CORPORA LUTEA SOLUBLE EXTRACT-WILSON.—A sterile solution of those constituents of corpus luteum which are soluble in physiological solution of sodium chloride containing in each cubic centimeter 0.02 Gm. of soluble matter in addition to sodium chloride and chlorbutanol as a preservative.

Actions and Uses.—See preceding article, Ovary.

Dosage.—One cc. daily in extreme cases; less according to individual cases.

Manufactured by The Wilson Laboratories, Chicago.

Ampoules Corpora Lutea Soluble Extract-Wilson: 1 cc. corpora lutea soluble extract-Wilson.

Corpora lutea soluble extract-Wilson is made by extracting desiccated corpus luteum with physiological solution of sodium chloride, and is adjusted to contain 0.02 Gm. of soluble extract in each cubic centimeter. The equivalent weight of dried corpus luteum represented by this amount of soluble extract is variable, ranging from about 0.06 Gm. to 0.18 Gm.

Corpora lutea soluble extract-Wilson is a straw colored liquid with the peculiar odor of corpora lutea.

CORPUS LUTEUM EXTRACT-LEDERLE.—A sterile solution of those constituents of corpus luteum which are soluble in water containing sodium chloride 0.85 per cent, sodium citrate 1 per cent and chlorbutanol 0.5 per cent. Each cc. contains 0.02 Gm. of soluble matter in addition to sodium chloride and sodium citrate and chlorbutanol as preservative.

Actions and Uses.—See preceding article, Ovary.

Dosage.—One c.c. intramuscularly every second day. In severe cases daily doses are said to be indicated.

Manufactured by the Lederle Antitoxin Laboratories, New York. No U. S. patent or trademark.

Ampules Corpus Luteum Extract-Lederle, 1 cc.

Corpus Luteum Extract-Lederle, 5 cc. vial.

Corpus luteum extract-Lederle is prepared by macerating corpus luteum-Lederle with three portions of a solvent consisting of an aqueous solution of sodium chloride 0.85 per cent, sodium citrate 1 per cent and chlorbutanol 0.5 per cent. The united extracts are clarified, analyzed for organic solids, and glycerin added so that it contains 5 per cent. The liquid is then adjusted so that it contains 0.02 Gm. of the soluble corpus luteum substance in 1 cc. and it is then sterilized by filtration through a Berkefeld filter.

STERILE SOLUTION OF LUTEIN-H. W. & D.—Each cc. contains the water soluble extractive of 0.2 Gm. of the fully developed corpora lutea of the hog freed of foreign material and desiccated. The extraction is freed of protein in physiological solution of sodium chloride.

Actions and Uses.—See preceding article, Ovary.

Dosage.—One cc. daily, intramuscularly.

Manufactured by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

Ampules Sterile Solution of Lutein-H. W. & D.: More than 1 cc. of sterile solution of lutein-H. W. & D.

Sterile solution of lutein-H. W. & D. is made by extracting corpora lutea of the hog freed of foreign material and desiccated with a solvent composed of equal parts of alcohol and water. The extract is freed of proteins by the addition of lead acetate and subacetate. After removal of the excess of lead, the liquid is freed of alcohol and the concentration adjusted so that each cubic centimeter shall represent the soluble extractive of 0.2 Gm. of the desiccated corpora lutea in physiological solution of sodium chloride.

PANCREAS

The pancreas is a gland having, in general, two functions: (1) It secretes into the intestine a digestive juice containing the enzymes trypsin, lipase and amylase; (2) it secretes into the blood a hormone, insulin, which regulates the process of carbohydrate metabolism. (For description of insulin, see under Insulin.)

When insulin fails to be secreted, the disease diabetes develops, in which the percentage of sugar increases in the blood (hyperglycemia) so that sugar overflows into the urine (glycosuria). The hyperglycemia is associated with a breakdown of the first and last stages in the metabolism of sugar, as revealed, respectively, by failure of glycogen to be deposited in the liver and by failure of the respiratory quotient to become increased when carbohydrate food is ingested. The depression in carbohydrate metabolism causes that of fats to become upset, so that ketone substances (acetone, acetoacetic and oxybutyric acids) appear, producing acidosis and, later, coma.

The exact mode of action of insulin is not clearly known. When artificially prepared, insulin, if administered subcutaneously, intravenously or intraperitoneally, causes a fall in the percentage of sugar in the blood. When this percentage falls below the kidney threshold in the diabetic patient, sugar disappears from the urine. If an overdose of insulin is given, the blood falls to a subnormal level, and characteristic symptoms are observed. The level at which these symptoms occur depends not only on the extent but also on the rate of fall. If the blood sugar has been persistently high and is rapidly reduced, hypoglycemic symptoms may appear at a much higher level of blood sugar than occurs when the fall is slower and more gradual. These symptoms are due to the diminished sugar in the blood, as shown by the fact that they are relieved by the replacement of the sugar by oral or intravenous administration.

Clinical assays conducted with uncomplicated diabetic patients on certain standard dietary regimens reveal that the Toronto insulin unit, will promote the metabolism of approximately 2 Gm. of glucose in such uncomplicated cases receiving standardized diabetic diets. The physician may, therefore, gauge his insulin dose with great precision. To do so, he must know how much glucose the patient will derive from his food and metabolism, and how much insulin the patient himself can provide from his insulin-making tissues. The latter may be determined by measuring the patient's ability to utilize carbohydrate without extra insulin. In any case, insulin injections must be made at regular intervals and must be supplemented by accurately weighed diets of known composition.

When properly employed, insulin is a specific in the treatment of diabetic coma and acidosis. It is of pronounced value in the management of diabetic patients undergoing surgery and of those with complicating infectious diseases. It makes possible freedom from glycosuria and good mental and physical vigor for patients with severe diabetes.

There is as yet no positive evidence that treatment with insulin will arrest the diabetic process by restoring the patient's antidiabetic function. In the severer cases, the evidence now available is against such an assumption. In the milder cases in which insulin has been used, the evidence is difficult of interpretation because such patients may show very marked improvement in their ability to utilize carbohydrate on dietary regulation alone.

Oral Administration of Pancreatic Preparations.—In diabetes, reliance on the oral administration of the pancreatic preparations thus far prepared has so little justification that such practice merits the most vigorous condemnation. Many reputed antidiabetic pancreatic preparations are on the market with claims that they are effective if taken by mouth. The most widely heralded of them have been subjected to the scrutiny of clinical tests controlled with simultaneous laboratory investigation. None of these thus tested have shown any effect on blood sugar or glycosuria. Completely negative results were obtained when these preparations were given in the doses recommended by their exploiters as well as in doses twenty times as large. The claim that such preparations exert, in some mysterious manner, a rejuvenating or stimulating action on the diseased pancreas is based on uncontrolled clinical observation.

Parathyroid Gland

Parathyroid preparations have been made from the dried gland for oral administration and by extracting substances from the gland for subcutaneous administration. The reports of success after oral therapy lack any conclusive evidence that this was dependent upon the use of the gland. No proof has been brought forward that the one definite effect that can be referred to the parathyroid gland (maintaining or raising the calcium concentration of the serum) has been produced by parathyroid preparations taken by mouth. To ascribe to the oral administration of parathyroid preparations improvement in conditions that are not definitely known to depend upon parathyroid disease, or deficiency, is illogical and misleading. In consideration of the accumulated evidence of the ineffectiveness of oral therapy with parathyroid, preparations of parathyroid designed for oral administration are not accepted for inclusion in this book. Recent investigations have shown that preparations which have a most powerful influence upon calcium metabolism may be made from the parathyroids of the ox. This substance is injected intramuscularly or subcutaneously. The calcium concentration of the serum of animals deprived of their parathyroid glands can be raised and maintained at a normal limit. By repeated doses it may be raised far beyond this, either in parathyroidectomized or normal animals: unless the dosage is carefully regulated, death may ensue. The preparations can be standardized according to their activity in raising the lowered calcium concentration. Treatment by these parathyroid preparations is rational and has been shown to be of value in tetania parathyreopriva and in infantile tetany. A continuance of their use in the former condition is doubtless necessary. In infantile tetany their employment would appear to be a temporary expedient until other measures have an opportunity to combat the fundamental underlying condition. In gastric tetany the calcium of the serum is normal. It is believed that its activity is interfered with. It has not yet been demonstrated sufficiently that this can be affected beneficially by parathyroid therapy.

The available clinical or scientific evidence does not permit an estimate of the ultimate usefulness of the parathyroid preparations. The near future should furnish evidence regarding their use in many different conditions. The danger of hypercalcemia which is easily induced by overdosage with an active preparation makes it imperative that clinical studies should be carefully controlled by accurate determinations of the serum calcium.

PARA-THOR-MONE-LILLY. — Parathyroid Extract-Collip.—A stable, aqueous solution containing the active principle or principles of the parathyroid gland of cattle and having the property of relieving the symptoms of parathyroid tetany and of increasing the calcium content of blood serum. It is standardized by its capacity to increase the blood serum calcium in normal dogs: one unit being defined as one one-hundredth of the amount of solution required to cause an increase of 0.005 Gm. of calcium (Ca) in the blood serum of a twenty kilogram dog, the increase in calcium being determined fifteen hours following the injection of the solution.

Actions and Uses.—Para-Thor-Mone-Lilly relieves the tetany of parathyroidectomized dogs and by its continued daily administration in small doses further attacks can be prevented. Experiments with animals show, however, that frequently repeated small doses are cumulative and may raise the blood serum calcium to dangerous levels. It must be recognized that para-thor-mone-Lilly is a most potent therapeutic agent and that its use may be attended with great danger unless due precautions are taken to avoid overdosage and the consequent development of hypercalcemia.

Para-Thor-Mone-Lilly is claimed to be a specific in tetania parathyreopriva and to have relieved acute and chronic tetany following thyroidectomy, so-called idiopathic tetany, and infantile tetany. The experimental clinical use of para-thor-mone-Lilly in conditions believed to be due to a low calcium content of the blood serum must be carried out with extreme caution.

Dosage.—In cases of true tetany where all the classical symptoms are fully developed, twenty to thirty units of para-thor-mone-Lilly may be administered. In severe cases, if necessary, this dose may be repeated two or three times within the first twenty-four hours, and the dosage then diminished as indicated by the condition of the patient. Doses ranging from ten to twenty-five units daily have been found sufficient to prevent the recurrence of tetany in chronic cases.

Para-Thor-Mone-Lilly may be administered subcutaneously. intramuscularly or intravenously.

Manufactured by Eli Lilly & Co., Indianapolis, under license from the University of Alberta. U. S. patent applied for. U. S. trademark 208,753.

Para-Thor-Mone-Lilly, P-20, 5 Cc.: **Each cc. contains 20 units.**

Fresh parathyroid glands of animals from which fat and connective tissue have been removed are ground and extracted with a hot acidified solution. After maceration for five hours, the glands are separated and again extracted with a hot acidified solution. The united extractions are cooled and the separated fat is removed. Alkali is added to neutralize the liquid, and the precipitate which forms at the neutral point is removed by filtration and dissolved in acidified water (p_H 2.5). The hydrogen ion concentration of the solution is then adjusted to approximately p_H 7 and the precipitate is again formed. This precipitate is dissolved in slightly acidified water, diluted approximately to the desired potency, filtered through a Berkefeld filter and submitted to standardization and sterility tests.

PARATHYROID HORMONE-SQUIBB.—A stable, aqueous solution containing the active principle or principles of the bovine parathyroid glands and having the property of relieving the symptoms of parathyroid tetany and of increasing the calcium content of the blood serum. It is standardized physiologically so that each cubic centimeter contains 20 units as defined by J. B. Collip, one unit being 1/100 of the amount necessary to increase by 5 mg. the blood serum calcium from 100 cc. of blood at the end of fifteen hours in a normal dog weighing 20 Kg.

Actions and Uses.—Parathyroid hormone-Squibb is specific for the tetany of normal or parathyroidectomized animals and is claimed to be equally specific for normal or parathyroidectomized man when injected subcutaneously for increasing the level of the blood serum calcium. It has been reported to be of value in infantile and maternal tetany, in lead poisoning, in idiopathic menstrual bleeding, in hemorrhage, and in relief of certain symptoms of tuberculosis. Due precaution should be taken to avoid the dangers of hypercalcemia that result from overdosage or from continued administration of small doses.

Dosage.—Parathyroid hormone-Squibb is administered subcutaneously, the dosage varying with the severity of the condition in which it is used and with the individual to whom it is administered. In chronic parathyroid tetany as much as 30 units, repeated if necessary two or three times in the first twenty-four hours, is suggested. After symptoms have cleared up, one injection every second day is considered adequate. In infantile tetany an initial dose of 10 units, followed by a similar dose if convulsions are not relieved, has been reported to be successful.

Manufactured by E. R. Squibb & Sons. No U. S. patent or trademark.

Parathyroid Hormone-Squibb, 5 cc.: Each cubic centimeter contains 20 units.

Parathyroid hormone-Squibb is prepared from fresh bovine parathyroid glands. The glands are minced and then digested by boiling with diluted hydrochloric acid. The insoluble residue is removed and the solution purified by fractionation with alcohol, acetone and ether. Final separation of the active principle is effected by isoelectric precipitation, the resultant product containing a minimum of pigmentary impurities and inert protein. The finished product is filtered, standardized physiologically, and adjusted to contain the desired number of Collip units.

PAROIDIN.—Parathyroid Extract-Hanson.—An aqueous solution containing the active principle or principles of the parathyroid gland of cattle and having the property of relieving the symptoms of parathyroid tetany and of increasing the calcium content of blood serum. It is standardized by its capacity to increase the blood serum calcium in parathyroidectomized dogs: one Hanson unit being defined as one one-hundredth of the amount of solution required to produce an increase of 0.001 Gm. of calcium (Ca) in the blood serum of parathyroidectomized dogs weighing approximately 15 Kg., the increase being determined after administrations to dogs (twenty-four hours after operation) of a sufficient quantity of solution to cause an average increase in blood serum calcium of 3 mg. within six hours.

Actions and Uses.—Paroidin is of pronounced and definite value in the treatment of tetany. It has been used experimentally, but with inconclusive results, in a number of other conditions, such as chorea, gastric and duodenal ulcers, and delayed healing of wounds. To guard against the serious consequences of hyperthyroidism, excessive doses of paroidin must be avoided and large doses of the preparation must not be administered without estimation of the blood serum calcium.

Dosage.—The average adult dose of paroidin is 0.2 to 0.4 cc. (30 to 60 Hanson units) every twelve hours for five or six days, never more than ten days in succession. Treatment should then be discontinued for a week or two, to be resumed if necessary. For children the initial dose should not exceed 0.1 to 0.2 cc. (15 to 30 Hanson units).

Paroidin is administered subcutaneously or intramuscularly; not intravenously.

Manufactured by Parke, Davis & Co., Detroit. U. S. patent applied for. U. S. trademark.

Paroidin, 5 cc.: Each cubic centimeter contains 150 Hanson units.

Fresh bovine parathyroid glands from which fat and connective tissue have been removed are ground and extracted with dilute hydrochloric acid (approximately 0.5 per cent) at the boiling temperature for about one hour. The mixture is then chilled, filtered to remove fat, and the filtrate treated with an aqueous solution of trinitrophenol to precipitate the active principle together with some protein. The precipitate is collected and extracted with acetone and alcohol containing hydrochloric acid. An excess of acetone is then added to precipitate the active fraction in the form of a water-soluble powder, which is then redissolved in water, diluted to the proper potency, sterilized, and submitted to standardization and sterility tests.

Pituitary Gland

Posterior Lobe.—The posterior lobe of the pituitary gland and the intermediate portion yield on extraction substances having a marked effect on plain muscle, especially that of the blood vessels and the uterus. The intravenous or subcutaneous injection of preparations of the posterior lobe is followed by an increase in blood pressure which is maintained over a considerable period. Injection of subsequent doses is followed by a similar effect unless repeated too soon after the first injection, when a fall in pressure may occur. The increase in pressure is due to an action on the smooth muscle of the vessels. The heart is not stimulated, and may be depressed, both through the vagus response to the high blood pressure and by a direct action on the heart muscle itself. Peristalsis is markedly increased by direct action on the muscular coat of the intestinal tract. The administration retards the secretion of urine to a marked degree during the first hour and a half and sometimes longer. There is some experimental evidence to show that the absorption of water from the gastrointestinal tract is delayed, thereby lessening the water available for secretion. The bladder musculature is stimulated, especially when it has been previously in an atonic condition. Pituitary substance does not increase the formation of milk, but the output is temporarily accelerated. The extract of the posterior lobe causes a marked constriction of the uterus by a direct stimulating action on the wall. This occurs in pregnant and in nonpregnant animals.

Solutions prepared from the posterior lobe injected subcutaneously are employed against uterine atony and in postpartum as well as in other forms of uterine hemorrhage. Pituitary preparations should not be injected during the first stage of labor because, if the cervix be not fully dilated, the energetic contractions may cause rupture of the uterus. It has also been recommended in shock and in various other conditions of temporary low blood pressure, but it would be ineffective in advanced shock and at best of only temporary benefit in incomplete shock. It is useful in intestinal paresis whether following abdominal operations or complicating pneumonia. It is also used in diabetes insipidus with temporary benefit. The extracts should always be injected hypodermically or intramuscularly.

Anterior Lobe.—Hyperactivity of the anterior lobe has been supposed to produce gigantism and acromegaly, for clinically both conditions have been accompanied by tumors of the pituitary. On the other hand, hypoactivity of the anterior lobe has been held responsible for the syndrome dystrophia adiposogenitalis, for this condition has also been found associated with tumors of that gland and experimental extirpation of the pituitary in dogs has often been accompanied by dystrophy, adiposity, and atrophy of the gonads and external genitalia.

More recently evidence has accumulated which indicates that the hormone of the anterior lobe is essential to normal growth and the development of the ovaries and testes, but that it has nothing to do with the other disturbances formerly attributed to abnormal functioning of the pituitary. The clinical evidence for this statement lies in the fact that a considerable number of cases of Fröhlich's syndrome have come to autopsy in which the pituitary has been histologically normal. It is also claimed that extirpation of the hypophysis in adult dogs and white rats without injury to the hypothalamus does not produce dystrophia adiposogenitalis. Extirpation in immature animals is followed by cessation of growth and sexual development, a condition which has been corrected in white rats by daily transplants of the anterior lobe of the pituitary or by daily intraperitoneal injections of appropriate amounts of the fresh extract of the anterior lobe of bovine glands taken from the animal directly after it has been slaughtered. This extract produces gigantism and it also impairs or prevents the growth and maturation of the ova when administered parenterally to normal young rats.

On the basis of this evidence the anterior lobe hormone might be expected to be useful only in cases of infantilism or genital atrophy attributed to hypo-activity of the pituitary.

The Council holds that extensive clinical trial has failed to establish the value of desiccated pituitary preparations for oral administration. This statement holds good for preparations of the anterior or of the posterior lobe.

AMPOULES OF PITRESSIN.—An aqueous solution containing the pressor and diuretic-antidiuretic principle of the posterior lobe of the pituitary gland (betahypophamine) containing less than 1 unit of oxytocic activity per cubic centimeter. Five-tenths per cent of chlorbutanol is used as a preservative. It is standardized by the method of Hamilton and Rowe (*J. Lab. & Clin. Med.* **2:**120 [Nov.] 1916) so that each cubic centimeter contains 20 pressor units (1 unit represents the pressor activity exhibited by 0.5 mg. of standard powdered pituitary-U. S. P.).

Actions and Uses.—Ampoules of pitressin are used for temporary stimulation of blood pressure, for increasing the muscular activity of the bladder and intestinal tract, also for antidiuretic effect in diabetes insipidus.

Experimental evidence has been obtained indicating that the product increases the blood sugar and it has been successfully employed to counteract overdoses of insulin in animals. No clinical studies to determine the value for this purpose have been reported so far. It has been suggested that the product may be of value either in conjunction with or supplementary to the use of epinephrine in the treatment of serum sickness and similar vasomotor disturbances, but no definite evidence on this point is as yet available.

Dosage.—From 0.3 to 1 cc. (5 to 15 minims) intramuscularly, repeated as may be indicated.

Manufactured by Parke, Davis & Co., Detroit. U. S. patent and trademark applied for.

Ampoules of Pitressin, 1 cc.: Each ampule contains more than 1 cc.

AMPOULES OF PITOCIN.—An aqueous solution containing the oxytocic principle of the posterior lobe of the pituitary gland (alphahypophamine) containing less than ½ unit of pressor activity per cubic centimeter. Five-tenths per cent of chlorbutanol is used as a preservative. It is standardized by the U. S. P. method for pituitary, each cubic centimeter containing 10 international units.

Actions and Uses.—Ampoules of pitocin are used to stimulate uterine contractions for obstetric purposes.

The use of the product may be particularly indicated in those cases in which increase of blood pressure or contractile action of the vascular system is undesirable. Its use is contraindicated in contracted pelvis and incomplete dilatation of the cervix.

Dosage.—From 0.3 cc. to 1 cc. (5 to 15 minims) intramuscularly. If used before delivery is completed, small doses are used, repeated if necessary in twenty to thirty minutes.

Manufactured by Parke, Davis & Co., Detroit. U. S. patent and trademark applied for.

Ampoules of Pitocin, 1 cc.: Each ampule contains more than 1 cc.

STERILE SOLUTION OF ANTERIOR LOBE PITUITARY EXTRACT-MULFORD.—An extract of the anterior lobe of the pituitary body of cattle, preserved by the addition of 0.5 per cent of phenol.

Actions and Uses.—See preceding article, Pituitary Gland.

Dosage.—Usually 1 cc. (15 minims).

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

Ampules Sterile Solution of Anterior Lobe Pituitary Extract-Mulford, 1 cc.

Sterile solution of anterior lobe pituitary extract-Mulford is prepared by macerating the anterior lobes of the pituitary of cattle with acidulated water. This is strained, filtered through porcelain, and preserved by the addition of 0.5 per cent of phenol.

Each cubic centimeter represents the extractive of 0.2 Gm. of fresh substance.

SOLUTION OF PITUITARY.—For description see the U. S. Pharmacopeia and Useful Drugs under Liquor Pituitarii.

Actions and Uses.—See preceding article, Pituitary Gland.

Dosage.—For use in obstetrical cases, from 0.2 to 1 cc. (5 to 15 minims); in surgical cases, from 1 to 2 cc. (15 to 30 minims), preferably by deep intramuscular injection or subcutaneously.

Pituitrin.—A slightly acid aqueous solution containing the water-soluble principles of the fresh posterior lobe of the pituitary body of cattle, approximately the same strength of Solution of Pituitary, U. S. P., preserved by the addition of chlorbutanol, each cubic centimeter containing 0.005 Gm. It is standardized (1) for oxytocic action by the method of the U. S. P. X, and (2) by its effect on blood pressure according to the method of Hamilton and Rowe (*J. Lab. & Clin. Med.* **2**:120 [Nov.] 1916).

Actions and Uses.—See preceding article, Pituitary Gland.

Dosage.—See Solution of Pituitary.

Manufactured by Parke, Davis and Co., Detroit. No U. S. patent. Trademark 76,722.

Ampoules Pituitrin, 0.5 cc.
Ampoules Pituitrin, 1 cc.

PARAFFIN FOR FILMS (SURGICAL PARAFFIN, PLASTIC PARAFFIN)

Paraffin intended for application to burns, etc., should be solid at body temperature, but more ductile and pliable than the official paraffin (Paraffinum-U. S. P.) and should be liquid at, or below, 50 C. A thin film when prepared and tested as described below should be pliable at or below 28 C. and ductile at or below 31 C. At body temperature (38 C.) it should be pliable, and adhere to, but permit ready detachment from, the skin.

Actions and Uses. — Paraffin for films acts mechanically. When applied to burns and denuded surfaces, it provides an air-excluding dressing which relieves pain, forming a soft, pliable splintlike covering to wounded surfaces, keeps the parts at a relatively uniform temperature, immobilizes the epidermal tissue, and may aid in the formation of new tissue by acting as a scaffolding for newly formed cells.

Paraffin for films is used mainly in the treatment of burns. It is said to be useful in the treatment of frostbite and chilblains, and for covering denuded surfaces. It is also employed to prepare paraffin covered bandages and to seal gauze dressings.

Application.—In the paraffin treatment of burns, the wound, after preparatory treatment, is dried and a thin coating of either liquid petrolatum or melted paraffin for films (at a temperature of about 53 C.) is applied by means of an atomizer or brush. This is followed by the application of a thin layer of absorbent cotton and then another layer of the melted paraffin. The dressing is finished by covering with cotton and bandaging.

A simple and equally efficient method consists in cutting a thin sheet of cotton or similar absorbent to a size somewhat larger than the wound. This is dipped into the melted paraffin, applied snugly to the wound, and covered with a bandage.

The melting point of paraffin for films is determined by the method of the U. S. Pharmacopeia, X, p. 445.

The pliability and ductility of paraffin is determined as follows: A little of the melted substance is poured on water having a temperature of about 40 C., so as to form a number of separate films. The temperature of the bath is then gradually lowered by the addition of cold water to determine the pliability and ductility (pliability test). The film while immersed in water is doubled on itself and the temperature of the water at which the film breaks sharply on *one* fold is observed (ductility test). The film is stretched while under water and the temperature of the water at which the film breaks sharply and evenly is noted.

A small surface of the forearm is painted with melted paraffin, covered with a thin layer of cotton, and another coat of paraffin painted on the cotton, and then dressed with cotton and bandage. After one hour, the film should remain attached to the skin, showing it adherent but easily removable.

PARRESINE.—A mixture composed of paraffin (melting point 48 to 49 C.), from 94 to 96 per cent; gum elemi, from 0.20 to 0.25 per cent; Japan wax, from 0.40 to 0.50 per cent; asphalt, from 0.20 to 0.25 per cent, and eucalyptol, 2 per cent. To this mixture is added from 0.5 to 1.0 per cent solution of alkannin in eucalyptol and a minute quantity of gentian violet, these being employed to bring the product to a standard color.

Actions, Uses and Dosage.—See preceding article, Paraffin for Films (Surgical Paraffin, Plastic Paraffin).

Prepared by The Abbott Laboratories, North Chicago. No U. S. patent. U. S. trademark 117,626.

Parresined Lace-Mesh Surgical Dressing: Net mesh gauze impregnated with, and containing, from 45 to 50 per cent of parresine.

PERBORATE PREPARATIONS

Analogous to the metallic peroxides (discussed under "Peroxides") are the inorganic peracids. Of these, perboric acid has been introduced into medicine in the form of sodium perborate. This preparation is decomposed by water into hydrogen peroxide and sodium metaborate. It is used similarly to the metallic peroxides.

PEROGEN BATH. — Oxygen Bath Salts, Perogen. — A preparation consisting of a catalyzer and sodium perborate capable of yielding 10 per cent of oxygen, the two substances being wrapped separately.

Actions and Uses.—The catalyzer is medicinally an indifferent substance. When the two substances are mixed with water, the catalyzer causes the liberation of the available oxygen of the sodium perborate. The oxygen bath thus obtained is said usually to reduce the blood pressure and pulse rate to a much greater extent than the ordinary bath. It is claimed to have marked tranquilizing and somnifacient effects.

Dosage.—One bath daily until twenty-four or forty-eight have been taken, with occasional intermissions.

Manufactured by Morgenstern & Company, New York. U. S. patent 969,073 (Aug. 30, 1910; expires 1927). U. S. trademark 75,982.

PEROXIDES

Hydrogen peroxide is a combination of two atoms of hydrogen with two atoms of oxygen, one of the latter being given off to oxidizable substances, leaving a residue of water. In the presence of catalase, a ferment found in all cells, it is readily decomposed. The liberated oxygen sometimes causes considerable effervescence. For this reason it is dangerous to inject it into closed body cavities or into abscesses from which the gas has not a free exit. Hydrogen peroxide solution (liquor hydrogenii dioxidi is official in the U. S. Pharmacopeia). This preparation is a germicide when diluted with not more than twice its volume of water. Diluted with an equal volume of water it destroys typhoid bacilli in two and one-half minutes.

Metallic Peroxides

Metallic peroxides are compounds in which the hydrogen of hydrogen peroxide has been replaced by metals, and which are readily decomposed with liberation of hydrogen peroxide, or of oxygen.

Actions and Uses.—Like hydrogen peroxide, the metallic peroxides depend for their value on the readiness with which a part of their oxygen becomes active. They are claimed to possess advantages over solution of hydrogen peroxide, because the oxygen is set free more gradually. Among themselves the metallic peroxides differ in their action in accordance with their solubility and the alkalinity produced by interaction of the peroxide with water. The action of peroxides is also affected by the nature of the metal which goes into solution when the peroxide is decomposed. Thus, the use of sodium peroxide is limited by the strong base formed when it dissolves in water.

Because of the strong oxidizing effects on the lower organisms, the peroxides have been recommended as a convenient means of sterilizing water.

CALCIUM PEROXIDE.—Calcii Peroxidum.—A mixture consisting essentially of calcium peroxide (the calcium salt, CaO_2, of hydrogen peroxide) and calcium hydroxide and carbonate, containing not less than 60 per cent calcium peroxide, equivalent to 13.3 per cent available oxygen.

Actions and Uses.—See preceding article, Peroxides.

Dosage.—From 0.06 to 0.3 Gm. (1 to 5 grains) in water or with sodium bicarbonate, two to three times daily.

Calcium peroxide is a light, cream-colored, odorless and tasteless powder. It is practically insoluble in water, but by such contact it is gradually decomposed into hydrogen peroxide and calcium hydroxide, the hydrogen peroxide being further decomposed by the alkaline calcium hydroxide with liberation of oxygen. It is decomposed by dilute acids with formation of a solution containing hydrogen peroxide.

If a few milligrams of calcium peroxide is shaken with 10 cc. of water and 1 drop of diluted sulphuric acid, and a few cubic centimeters of ether added, the subsequent addition of a drop of potassium dichromate solution will produce a blue color in the aqueous layer. On shaking the mixture, the blue will pass into the ethereal layer. If 1 Gm. of calcium peroxide is dissolved in 25 cc. of diluted nitric acid and 2 cc. of tenth-normal silver nitrate added to the solution and the resulting precipitate filtered off, the further addition of a few drops of silver nitrate solution to the filtrate will produce no turbidity. If 1 Gm. of calcium peroxide is exposed to the full heat of a Bunsen flame for five minutes, then dissolved in 25 cc. diluted hydrochloric acid and the solution made up to 100 cc., a solution will result which will conform to the following tests: Ten cc. of the solution, to which ammonium hydroxide in excess has been added, will yield a white precipitate on the addition of ammonium oxalate solution. Ten cc. of the solution saturated with hydrogen sulphide will yield no precipitate, nor become colored. Ten cc. of the solution will yield not more than a turbidity on the addition of barium chloride solution. Ten cc. of the solution, after addition of a slight excess of ammonium hydroxide and acidification with acetic acid, will yield no turbidity on the addition of potassium dichromate solution. If from 0.2 to 0.3 Gm. of calcium peroxide, weighed into a flask, is shaken with 25 cc. of water, then 25 cc. of diluted hydrochloric acid added, the titration of this solution with tenth-normal potassium permanganate will indicate the presence of not less than 60 per cent of calcium peroxide.

Calcium Peroxide-Merck.—A brand of calcium peroxide-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.

Calcium Peroxide-R. & H.—A brand of calcium peroxide-N. N. R.

Manufactured by the Roessler & Hasslacher Chemical Company, New York.

SODIUM PEROXIDE. — **Sodii Peroxidum.** — The sodium salt of hydrogen peroxide containing at least 90 per cent of sodium peroxide, Na_2O_2, equivalent to 18.4 per cent of available oxygen.

Actions and Uses.—Sodium peroxide is not used internally, but has been used in acne, applied in the form of a paste prepared with liquid paraffin, or as a soap to remove comedones.

Sodium peroxide occurs in the form of a white, or yellowish, amorphous powder. It is soluble in water, with decomposition and evolution of heat, forming an alkaline solution and liberating oxygen. It dissolves in cold dilute acids, forming a solution of hydrogen peroxide. When heated, sodium peroxide becomes darker, but on cooling resumes its original color. It does not react with alcohol, but it ignites ether on contact. A mixture with red phosphorus explodes under pressure on being struck. It is an extremely powerful oxidizing agent.

Sodium peroxide should not respond to tests for sulphates, chlorides, phosphates, nitrates and heavy metals. If 1 Gm. or 1.5 Gm. of sodium peroxide is weighed and gradually added with constant stirring to 950 cc. of diluted sulphuric acid (1 per cent) and the solution made up to 1,000 cc., the titration of 100 cc. of this solution with tenth-normal potassium permanganate will indicate the presence of not less than 90 per cent sodium peroxide.

Sodium Dioxide, Dental-R. & H.—A brand of sodium peroxide-N. N. R., containing at least 90 per cent of sodium peroxide, and iron not to exceed 0.006 per cent.

Manufactured by the Roessler & Hasslacher Chemical Company, New York. No U. S. patent or trademark.

Sodium Peroxide-Merck.—A brand of sodium peroxide-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.

Sodium Peroxide-R. & H.—A brand of sodium peroxide-N. N. R.

Manufactured by the Roessler & Hasslacher Chemical Company, New York.

Oxone. — Oxone is a proprietary name applied to fused sodium peroxide containing a fractional percentage of a catalytic agent. It is said to yield its entire content of available oxygen in gaseous form, on contact with water.

Manufactured by the Roessler & Hasslacher Chemical Company, New York. U. S. patent 788,256 (April 25, 1905; expired) and 884,563 (April 14, 1908; expired). U. S. trademark 46,673.

PETROLATUM.—For description see the U. S. Pharmacopeia and Useful Drugs under Petrolatum.

Petrobran.—Each 100 Gm. contains: petrolatum, 74 Gm.; bran, 22 Gm., with powdered licorice and "oil of pineapple" (ethyl butyrate) sufficient to flavor.

Prepared by Sargent's Drug Store, Chicago. No U. S. trademark.

PHENETIDIN DERIVATIVES

The phenetidins (derivatives of para-aminophenol $C_6H_4(NH_2)(OH)$, 1:4) comprise chemical relatives of aniline (aminobenzene). The members of this group have similar properties and are more or less active, according as they undergo decomposition in the system, so as to yield either para-aminophenol or acetylaminophenol. They have a more or less pronounced action on the blood, by which they produce hemolysis and destruction of the red blood corpuscles. They also act as heart depressants.

Acetphenetidin and its congeners are antipyretics and analgesics. They are extensively employed for the relief of pain, but for this purpose they should be used with caution in consideration of their poisonous properties.

They have also been considerably employed for the reduction of temperature in fever. Every newly discovered product related to acetphenetidin has been heralded as a "safe" antipyretic and free from poisonous effects on the blood and heart. Invariably, extended clinical experience has shown that all these preparations are, to a greater or less degree, hemolytic and depressing to the circulation. Hence their employment in the infectious fevers should be most cautious.

ACETPHENETIDIN.—For description see the U. S. Pharmacopeia and Useful Drugs under Acetphenetidinum.

Actions and Uses.—See Useful Drugs.

Phenacetin.—A name applied to acetphenetidin. See the U. S. Pharmacopeia. The tests of identity and purity prescribed by the United States Pharmacopeia under acetphenetidin should apply to the product dispensed under this title.

PHENACAINE.—See Anesthetics, Local.

PHENETSAL.—Phenetsalum.—Salophen.—Acetyl-*p*-aminophenyl Salicylate.—Acet-*p*-aminosalol. — 1 : 4-Acetaminophenyl Salicylate.—$C_6H_4.OH.CO.O.C_6H_4(NHCH_3CO)$. The salicylic acid ester of 1 : 4-acetaminophenol, $C_6H_4(NHCH_3CO)(OH)$.

Actions and Uses.—The actions of phenetsal resemble those of phenyl salicylate (salol). It is not changed in the stomach, but is broken up in the intestine, liberating salicylic acid and paramidophenol (which is less toxic than phenol). It acts as an antirheumatic, antipyretic, antiseptic and analgesic. It is said to be useful in rheumatism, gout, typhoid fever, and as an intestinal antiseptic, in diarrhea and dysentery. Externally, it has been applied in psoriasis and other itching skin diseases.

Dosage.—From 0.3 to 1 Gm. (5 to 15 grains), in powder, wafers or capsules. Externally, in 10 per cent ointment.

Phenetsal forms small, white, crystalline leaflets or powder, odorless and tasteless, melting at from 187 to 188 C. It is almost insoluble in cold water, more soluble in warm water, freely soluble in watery solutions of the alkalis and in alcohol, ether and benzene, but not in petroleum benzin.

If its alkaline solution is boiled, it gradually becomes blue; on continuing the boiling the color is discharged, but is again produced on cooling and exposure to air. On the addition of ferric chloride to the alkaline solution, the violet color characteristic of salicylic acid is produced, but a simple aqueous solution of phenetsal does not react with ferric chloride and should not be changed by silver nitrate. It forms a colorless solution with concentrated sulphuric acid.

It is incompatible with alkalis, which decompose it.

Salophen.—A brand of phenetsal-N. N. R.

Manufactured by The Bayer Company, Inc., Rensselaer, N. Y. (Winthrop Chemical Company, N. Y., distributor). No U. S. patent. U. S. trademark 20,759.

Winthrop Tablets of Salophen, 5 grains.

Salophen-Morgenstern.—A brand of phenetsal-N. N. R.

Manufactured by Morgenstern & Company, New York. No U. S. patent or trademark.

PHLORHIZIN. — Phlorhizinum. — Phlorizin. — $C_{21}H_{24}O_{10}+2H_2O$.—A glucoside from the root of the apple, pear, cherry, etc.

Actions and Uses.—Phlorhizin destroys malarial parasites *in vitro.* When administered to man or animals, it produces glycosuria of renal origin. Polyuria is also produced. It has been recommended as an antiperiodic in malaria; but its use in this disease is not justified in view of the possible injury to the kidney which it may cause. It is used as a means of testing the functional activity of the kidney.

Dosage.—To test the permeability of the kidney, 0.005 Gm. (1⁄12 grain) is dissolved in 1 cc. (15 minims) of a 0.5 per cent solution of sodium carbonate and injected hypodermically. Glucose should appear in the urine in from fifteen minutes to one-half hour and the secretion of sugar should continue for from two to four hours. The test gains in diagnostic value if the urine of each kidney is collected separately. Phlorhizin may be given by mouth in pills massed with glucose syrup or suspended in a mixture with acacia or tragacanth. The internal dose is from 0.3 to 0.6 Gm. (5 to 10 grains).

Phlorhizin occurs as minute white, slightly pinkish crystals, of a silky texture, or as a pale yellow, light crystalline powder, odorless and having a bitter, but later a sweet, taste. It is sparingly soluble in cold, but freely soluble in hot water, from which it crystallizes on cooling. It is soluble in alcohol (1 in 4) and sparingly soluble in ether. The solutions are levogyrate. At 100 C it loses water and at about 107 C. melts. When heated to about 130 C., it becomes solid again and melts again at about 170 C. At about 200 C. it assumes a red color, due to the formation of rufin. Boiled with dilute acids, it is converted into sugar, phlorose and phloretine. Exposed to air in the presence of ammonia, it assumes a purple color. Cold concentrated sulphuric acid dissolves it to a yellow solution and at from 25 to 50 C. the solution becomes red.

Phloridzin-Merck.—A brand of phlorhizin-N. N. R.
Merck & Co., Inc., Rahway, N. J., distributor.

PSYLLIUM SEED.—Semen Psyllii.—The seed of *Plantago Psyllium* and related species of *Plantago.*

Actions and Uses.—Psyllium seed, by virtue of its indigestibility and mucilaginous character, acts as a mild laxative.

Dosage.—From 4 to 15 Gm. (1 to 4 drachms) one to three times a day. Psyllium seed may be mixed with orange juice or prune juice and eaten without mastication, or the dose may be mixed with a little hot water and the resulting gelatinous mass spread on bread or taken with other food.

Psyllium seeds are ovoid, about 3 mm. in length and from 1 to 1.5 mm. in width; convex on one side and concave on the other; dark reddish brown, inodorous and almost tasteless. When psyllium seed is mixed with an equal bulk of water, a mucilaginous mass is formed by virtue of the mucilage which exudes from the cell wall.

PYRAZOLON DERIVATIVES

The preparations in this group are used for their antipyretic and analgesic action. There is reason to believe that they have less tendency to disintegrate the red blood corpuscles than have the phenetidine compounds, but in other respects they are open to the same objections. On taking small doses, some susceptible individuals experience nervous and circulatory depression, while after large doses instances of collapse have been reported.

The following pyrazolon derivatives are included in New and Nonofficial Remedies:

Antipyrine salicylate (salipyrin), which is a simple salt of antipyrine with salicylic acid, said to possess the therapeutic properties of both these constituents.

Melubrin, a complex synthetic differing from antipyrine in that a sodium amino-methyl sulphite has replaced the hydrogen atom of the pyrazolon group. In this it is asserted that the toxicity is very much reduced.

Amidopyrine (pyramidon) chemically known as dimethylamino antipyrine.

Antipyrine Compounds and Derivatives

Antipyrine, phenyldimethylpyrazolon, is a weak base which unites with acids to form unstable salts that hydrolyze readily when dissolved in water, separating into the components. The therapeutic activity of these compounds represents a combination of the actions of the acid and the base.

SALIPYRIN. — Antipyrinae Salicylas. — Antipyrine Salicylate.—$C_{11}H_{12}N_2O.C_6H_4OH.COOH$.—A weak chemical combination of antipyrine and salicylic acid.

Actions and Uses.—This compound possesses the properties of both antipyrine and salicylic acid and combines the analgesic power of the one with the antirheumatic action of the other. It has been used with good results in sciatica, rheumatic fever, chronic rheumatism, influenza, pleurisy, dysmenorrhea, etc.

Dosage.—From 0.3 to 2 Gm. (5 to 30 grains) in cachets or capsules.

Manufactured by J. D. Riedel, Aktiengesellschaft, Berlin, Germany (Riedel & Co., Brooklyn). U. S. patent expired. U. S. trademark 76,952.

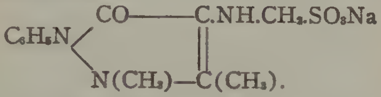
Salipyrin Tablets, 7½ grains.

Salipyrin occurs as a white, coarsely crystalline powder, or in hexagonal tubular crystals, melting at from 91 to 92 C.; odorless, slightly sweet; soluble in 200 parts of cold and 40 parts of boiling water; readily soluble in alcohol, less readily in ether. It is decomposed by acids with the elimination of salicylic acid, and by alkalis with the elimination of antipyrine.

An aqueous solution of salipyrin is rendered milky by tannic acid, then colored green by the addition of a few drops of fuming nitric acid. It is colored deep red by ferric chloride solution, passing to violet red on copious dilution with water. It is not affected by hydrogen sulphide. It is decomposed by acids, alkalis and tannins.

Transfer about 1 Gm. of salipyrin, accurately weighed, to a separator; treat with 25 cc. of water and 10 cc. of sodium hydroxide solution and extract with chloroform: the latter on evaporation yields a residue which, when dry, weighs from 0.57 to 0.58 Gm., melts at 113 C., and responds to the tests for antipyrine. Acidify the solution remaining in the separator and extract with chloroform and allow the chloroform to evaporate: a residue of white needle-like crystals remains, which, when dry, melts at from 155 to 156 C. and responds to the tests for salicylic acid. Dissolve from 0.5 to 1 Gm. of salipyrin in 50 cc. of diluted alcohol; add a few drops of phenolphthalein; titrate this solution with tenth-normal alkali: the presence of not less than 32.1 per cent of salicylic acid is indicated.

MELUBRIN.—Sodium 1-Phenyl-2,3-Dimethyl-5-Pyrazolon-4-Amidomethansulphonate.



The sodium salt of 1-phenyl-2,3-dimethyl-5-pyrazolon-4-aminomethansulphonic acid, differing from antipyrine, $C_{11}H_{12}N_2O$, in that a sodiumaminomethansulphonate group, $NH.CH_2.SO_3Na$, has replaced a hydrogen atom of the pyrazolon group.

Actions and Uses.—It is claimed that melubrin in ordinary or even large doses is not toxic. In moderate doses, it is said to have almost no effect on the circulation or respiration. It acts as a powerful antipyretic in fever and it is analgesic.

Melubrin is said to be useful in painful affections, such as sciatica and other neuralgias, and as an antipyretic in various febrile affections. It is said to have effects similar to those of the salicylates in acute rheumatism.

Dosage.—From 1 to 2 Gm. (15 to 30 grains). The larger doses are recommended for the treatment of rheumatism. It is claimed that as much as 10 Gm. (150 grains) may be given daily.

Manufactured by Farbwerke, vorm. Meister, Lucius and Bruening, Hoechst, a. M., Germany (H. A. Metz Laboratories, Inc., New York). U. S. patent 1,056,881 (March 5, 1913; expires 1930). U. S. trademark 88,562.

Melubrin is prepared by allowing a solution of formaldehyde bisulphite to act on 1-phenyl-2,3-dimethyl-4-amino-pyrazolon, and purifying the resulting product by recrystallization.

It is a white, odorless, almost tasteless crystalline powder, readily soluble in water, but slightly soluble in alcohol. The aqueous solution is neutral in reaction but unstable.

If about 0.2 Gm. of melubrin dissolved in 5 cc. of water is boiled with 3 cc. of diluted hydrochloric acid, sulphur dioxide and formaldehyde will be liberated. If half of the solution thus formed is treated with 3 drops of sodium nitrite solution and 5 cc. of an alkaline solution of betanaphythol, a red precipitate will be produced. If the remainder of the solution is treated with 1 Gm. of sodium acetate and 15 cc. of a saturated aqueous benzaldehyde solution a yellowish white, flocculent precipitate will be formed which, when washed and dried, will melt at 173 C. If a small quantity of melubrin is moistened with hydrochloric acid, it will respond to the flame test for sodium. If a 10 per cent aqueous solution of melubrin is made alkaline with ammonia, saturation with hydrogen sulphide should produce no change. If 0.5 Gm. of melubrin is thoroughly mixed with 4 Gm. of sodium nitrate and gradually heated, 4 cc. of concentrated sulphuric acid added to the resulting mass, and the mixture heated until no further white fumes are produced, the resulting substance powdered and mixed with 10 cc. of saturated hydrochloric acid solution of stannous chloride, no darkening will occur within one hour. If from 0.4 to 0.5 Gm. of melubrin is weighed to a platinum dish, treated with dilute sulphuric acid, and heated to constant weight, the sodium sulphate thus formed will weigh from 0.2160 to 0.2250 Gm. for each gram of material used, representing a sodium content of from 6.99 to 7.28 per cent.

Amidopyrine and Amidopyrine Derivatives

AMIDOPYRINE.—For description see the U. S. Pharmacopeia under Amidopyrina.

Actions and Uses.—Amidopyrine acts as an antipyretic and anodyne, similarly to antipyrine, but is effective in smaller doses. The action, while somewhat slower at the beginning, is more lasting. It is claimed to be comparatively free from harmful influences on the blood, heart or kidneys. It is said to be useful, particularly in the chronic fevers of tuberculosis, as well as in the acute febrile conditions incident to typhoid fever, erysipelas and pneumonia. In the treatment of infectious fevers, it, as other antipyretics, should be cautiously employed. See general article, Phenetidin Derivatives.

Dosage.—From 0.3 to 0.4 Gm. (5 to 6 grains), most conveniently in the form of tablets, a single dose usually sufficing for twenty-four hours.

Pyramidon.—A brand of amidopyrine-U. S. P.

Manufactured by H. A. Metz Laboratories, Inc., New York. U. S. patent expired. U. S. trademark.

Pyramidon Tablets, 5 grains.

QUINIDINE

Quinidine is obtained from cinchona bark as a by-product in the manufacture of quinine, to which it is closely related, being the stereoisomer of quinine.

Actions and Uses.—Quinidine, like quinine, is a protoplasm poison. It affects protozoa more than bacteria but less powerfully than quinine. At one time it was used, to some extent, as a substitute for quinine because it was then much the cheaper preparation.

Quinidine acts upon the heart in such a manner as to bring about cessation of fibrillation of the auricles in a certain proportion of instances. Quinidine and other cinchona alkaloids are the only drugs known to have this specific effect. The pharmacology of the drug has been extensively investigated. It has been shown that quinidine increases the refractory period of the auricular muscle and decreases its irritability and the rate of conductivity. Its action is both upon the auricular muscle and through the vagus. In ordinary doses the heart is slowed and the auriculo-ventricular conduction time is lengthened. Quinidine is used to restore the normal rhythm of the heart in cases of auricular fibrillation. This has been brought about in approximately 50 per cent.

of the reported cases in which the drug has been used. It is apparently most efficacious in the cases of fibrillation of short duration or of the paroxysmal type. It may also stop fibrillation of several years' duration. It is least effective in cases of fibrillation with marked cardiac insufficiency. Quinidine is not without some unpleasant and even dangerous effects. Some patients appear much more susceptible to its toxication than others. The untoward symptoms brought about by its use in these patients are nausea, vomiting, convulsions, palpitation, headache, faintness and flushing. In most cases following the administration of the drug, the pulse increases in rapidity before the normal rhythm is established. In some cases the effect of the drug is restricted to this alteration of rhythm. In a few instances, such serious results as rapid idioventricular rhythms (ventricular tachycardia) have been initiated during the course of therapy. Toxic effects may appear after the establishment of a normal rhythm. Some cases have been reported in which sudden death occurred a short time after the drug had been stopped. The drug is rapidly eliminated and it appears that no cumulative effect can take place. It has no known permanent effect.

Dosage.—Quinidine is generally administered as quinidine sulphate. Commonly 0.2 Gm. (3 grains) of quinidine sulphate is given as a preliminary dose and is repeated after two hours to determine the patient's susceptibility to the drug. If there are no symptoms following this preliminary dose, therapeutic administration is begun on the following day when from 0.2 Gm. to 0.4 Gm. (3 to 6 grains) is given from three to five times daily, for one to three days. As a rule, if the establishment of the normal rhythm can be effected, the change occurs after from one to three days' treatment. The maximum dose per day advised by most authors is from 1 to 2 Gm. (15-30 grains). If toxic symptoms occur, the administration of the drug should be discontinued.

QUINIDINE.—Quinidina.—An alkaloid, $C_{20}H_{24}O_2N_2+2H_2O$, obtained from the bark of various species of *Cinchona.*

Actions and Uses.—See preceding article, Quinidine.

Dosage.—See preceding article, Quinidine.

Quinidine occurs in white crystals or as an amorphous, white powder; odorless; taste, intensely bitter and persistent; efflorescent in dry air.

Quinidine is very slightly soluble in water; soluble in alcohol and ether; freely soluble in chloroform; very slightly soluble in petroleum benzin.

The saturated aqueous solution of quinidine is alkaline to litmus and its alcoholic solution is dextrorotatory. A solution of quinidine in diluted sulphuric acid (1 in 1,000) shows a strong blue fluorescence.

Quinidine loses its water of hydration at 100 C. The dried alkaloid melts at about 168 C.

Add a few drops of bromine water to 10 cc. of an aqueous solution of quinidine (1 in 1,000), prepared with just sufficient diluted sulphuric acid to produce complete solution, and follow with ammonia water in slight excess. The liquid acquires an emerald-green color.

Dissolve about 0.1 Gm. of quinidine in 15 cc. of hot water containing a few drops of diluted sulphuric acid; cool the solution; add 1 cc.

of silver nitrate solution and stir the mixture with a glass rod. A white, crystalline precipitate forms after a short interval (*distinction from many other alkaloids*).

Dissolve about 0.1 Gm. of quinidine in 10 cc. of warm water, containing a slight excess of diluted hydrochloric acid; add an excess of potassium iodide solution and agitate: an orange yellow, crystalline precipitate forms after an interval (*distinction from quinine*).

Dissolve 0.5 Gm. of quinidine in 15 cc. of boiling distilled water, with just enough sulphuric acid to form a solution neutral to litmus paper, and add 5 cc. of potassium iodide solution. Agitate the mixture gently; cool it to 15 C., and keep it at this temperature for one hour, with occasional stirring: a white precipitate is formed (*difference from quinine*). Filter out the precipitate and add 2 drops of ammonia water to the filtrate: not more than a slight turbidity results (*limit of other cinchona alkaloids*). Care must be taken to have the liquid perfectly neutral after the addition of the potassium iodide solution; if slightly acid, very dilute ammonia water must be added, drop by drop, with constant stirring until exact neutrality to litmus is attained.

A solution of about 0.1 Gm. of quinidine in 5 cc. of sulphuric acid is not darker than pale yellow (*organic impurities*).

Incinerate about 1 Gm. of quinidine, accurately weighed: the ash does not exceed 0.1 per cent.

Dry about 1 Gm. of quinidine, accurately weighed, to constant weight at 100 C.: the loss does not exceed 11 per cent.

Quinidine-Mallinckrodt.—A brand of quinidine-N. N. R.

Mallinckrodt Chemical Works, St. Louis, distributor. No U. S. patent or trademark.

Quinidine-N. Y. Q.—A brand of quinidine-N. N. R.

Manufactured by the New York Quinine and Chemical Works, New York. No U. S. patent or trademark.

Quinidine-Merck.—A brand of quinidine-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

QUINIDINE SULPHATE.—For description see the U. S. Pharmacopeia and Useful Drugs under Quinidinae Sulphas.

Actions and Uses.—See preceding article, Quinidine.

Dosage.—See preceding article, Quinidine. Quinidine sulphate may be administered in the form of cachets, capsules, pills or tablets.

QUININE DERIVATIVES

The action of quinine is essentially the same in all its compounds. The official salts have the disadvantage of the bitter taste, and of producing a local action on the stomach and other tissues. To obviate these difficulties, insoluble compounds like the alkaloid or the tannate have been used, since these pass the mouth and stomach without offending the taste or disturbing the stomach. The same object is obtained more or less completely in a number of synthetic compounds in which the quinine radical is combined with other radicals, such as those of carbonic acid, to form insoluble, and therefore tasteless, esters. In the intestines these esters are broken up more or less rapidly into the alkaloid quinine and the other components. The rapidity with which this decomposition occurs will determine to a large extent the intensity of the therapeutic effect and the liability to produce cinchonism.

Some of the esters also contain other therapeutically active radicals (phenetidine, salicyl, etc.). When liberated these produce their characteristic effects; but it is doubtful whether the combinations of several therapeutically active radicals in fixed proporitons are superior to simple mixtures of the ingredients.

QUININE SULPHATE.—For description see the U. S. Pharmacopeia and Useful Drugs under Quininae Sulphas.

Coco-Quinine: Each 100 cc. contains quinine sulphate, 2.19 Gm. (10 grains per fluidounce), suspended in a syrup flavored with chocolate, yerba santa and vanillin, and containing sodium benzoate, 0.18 Gm. per 100 cc. and alcohol, 4 per cent.

Prepared by Eli Lilly & Co., Indianapolis. U. S. trademark 174,144.

Syrup of Quinine with Chocolate: Each 100 cc. contains in suspension: quinine sulphate, 2.15 Gm. (10 grains per fluidounce); chloroform as a preservative 0.43 cc. (2 minims per fluidounce), in a syrup flavored with yerba santa, chocolate and vanillin.

Prepared by the H. K. Mulford Company, Philadelphia.

QUININE ETHYLCARBONATE.—For description see the U. S. Pharmacopeia under Quininae Aethylcarbonas.

Actions and Uses.—Quinine ethylcarbonate is used in place of quinine sulphate and similar soluble quinine salts when a practically tasteless quinine compound is preferred.

Dosage.—The same as that of quinine sulphate.

RADIUM AND RADIUM SALTS

Radium is a bivalent metallic element closely related to barium. It is very active chemically, and, consequently is difficult to isolate in its metallic state and, after isolation, to keep pure, since it reacts with air, forming the oxide and nitride, and finally the carbonate. Because of this activity, it is produced only in the form of its salts, principally the soluble bromide and chloride, and the insoluble carbonate and sulphate.

The therapeutic value of radium is due to its radioactivity, which is defined as "the property of spontaneously emitting radiations, part of which are capable of passing through plates of metal and other substances opaque to ordinary light, and which have the power of discharging electrified bodies." All the radioactive elements disintegrate spontaneously. The transformation of the atom is accompanied by the emission of so-called "rays," which consist of alpha and beta particles and gamma rays. This spontaneous transformation of radium continues at a regular rate, which is independent of the physical state or chemical combination of the radium atom in the molecules of its compounds. It is changing at such a rate that in about 1,700 years half of any quantity will have changed.

In the transformation of radium, a series of products is formed, the first of which is the gas niton, or radium emanation. This is a heavy inert gas having a density 111 times that of hydrogen. It has a half period of 3.85 days, that is, one half of the emanation decays in that length of time. It emits weak alpha rays with the resulting formation of Radium A; and in a similar manner, by the successive loss of an alpha or beta particle, or both, Radium B, C_1, C_2, C', D, E, and F are formed. Gamma rays usually accompany the emission of a beta particle. The Radium C group gives off the most penetrating rays, so that whether a radium salt or radium emanation is used, practically all the useful rays come from this group.

Measurements and Units.—The ionization produced in gases by the rays from radioactive substances is used to determine the quantity of active material. By observation of the rate of movement of the leaf in a calibrated electroscope, due to the leakage of the charge through the ionized gas, the intensity of the radiation can be determined.

Radium preparations are valuable in proportion to their content of radium. The content of radium may be found with a high degree of accuracy by the measurement of the intensity of its gamma radiation, or by the measurement of the rate at which it produces emanation, two official methods of the United States Bureau of Standards. The first consists in the measurement of the rate of discharge of an electroscope by the gamma rays which have passed through a sheet of lead, 1 cm. thick, which removes the beta rays, and minimizes the effect of the relatively soft gamma radiation from Radium B. This method is accurate to a fraction of 1 per cent, but is not suitable for quantities of radium of less than 0.1 mg. The second method, the measurement of the rate of production of the emanation, is used for radium solutions and slightly active solids; in this procedure it is first necessary to dissolve the solid. The activity of the emanation that accumulates in a given time is compared by means of an emanation electroscope with the activity of the emanation that accumulates in a given time from a standard radium solution.

The units commonly used for expressing radioactivity are:

1. Milligrams, and micrograms of radium element (a microgram is 0.001 mg.).

2. Curies, millicuries, and microcuries of radium emanation, the curie being the quantity of emanation present when 1 Gm. of radium element is in equilibrium with its disintegration products.

3. Mache units. It is generally considered that 2,700 mache units express the equivalent of one microcurie of radium

emanation. The use of the unit for denoting quantities of radium emanation should be discouraged, because (1) a number of definitions for this unit are in use; (2) it denotes concentration rather than quantity, and (3) it is too small for general use.

The terms compounded with gram are used in reporting analyses of the actual radium content of radium preparations. The terms compounded with curie express the quantity of radium emanation.

Purchasers of radium salts are often concerned about the content of mesothorium; but the Bureau of Standards has found no evidence of an appreciable percentage of mesothorium in any preparations from domestic producers that it has tested over intervals of time greater than six months.

A letter from the director of the Bureau of Standards, (*J. A. M. A.* **74**:1731 [June 19] 1920) contains these statements:

> The carnotites, from which the domestic radium is produced, are known to contain only a negligible amount of mesothorium. Tests made on radium produced from such ore gave no evidence of the presence of mesothorium, and were such as to indicate that the mesothorium present cannot exceed 0.2 per cent of the radium content of the material. Consequently, it is quite safe to assume that the radium produced from these deposits will be practically free from mesothorium unless the latter product is deliberately added. This is a matter over which the producer has control and concerning which he can speak with confidence. It is customary for the domestic producers of radium to guarantee that their product is practically free from mesothorium, and such a guarantee might well be requested by the purchaser.
>
> Although the examination of a hermetically sealed radium preparation for the presence of mesothorium forms no part of the routine measurement of such materials by the bureau, such examination will be made when requested under conditions that justify the work. These examinations are laborious, require the opening of the preparation and the removal of some of the salt, and involve the risk of a considerable loss of material. As in the case of all tests made by the bureau, the applicant must furnish the material used, assume the risk of loss, and pay a fee commensurate with the labor involved.

Rays.—Radium rays are divided into three groups, alpha, beta and gamma, which differ in velocity and penetrating power. The alpha rays consist of electropositively charged atoms of helium; the beta rays are particles of negative electricity, called electrons, which are identical in all respects to the cathode rays in a roentgen-ray tube. Both kinds of rays have enormous velocities, ranging from one tenth of the velocity of light for some alpha rays to nine tenths for some beta rays. The alpha rays are feebly penetrating because of their comparatively large size, and are stopped by a sheet of paper. These rays produce more ionization in gases through which they pass than either of the others. The beta rays are more penetrating than the alpha rays, being able to produce ionization after passing through several thicknesses of paper or thin sheets of metal or glass. Ninety per cent of the heterogeneous beta rays from radium preparations are absorbed by 2 mm. of aluminum or by 5 mm. of muscle tissue. The gamma rays are electromagnetic vibrations in the ether, identical with roentgen rays, but of shorter wave length and hence of higher penetrating power. It requires 7.6 cm. of muscle to absorb 50 per cent of these rays.

Emanation.—Radium emanation, to which the term "radon" has been applied in scientific literature, is set free continuously from slightly acidulated solutions of radium salts, from which it can be collected and purified either chemically, as in Duane's apparatus, or by liquid air, as in Rutherford's apparatus. It is used mostly in place of the radium salts when the quantity of radium is sufficient to warrant the installation of an emanation apparatus. The emanation is sealed in short capillary glass tubes which are placed in a metal container, the purpose of which is to stop the soft beta rays and to protect the tubes from breakage, or they may be inserted directly into a tumor if their emanation content is sufficiently small. The dosage in millicurie hours is then found by multiplying the quantity of emanation by 133.3. A measuring device of some sort is also necessary in order that the strength of the tubes may be determined.

The emanation is occasionally dissolved in water for internal or external use, or is set free in an emanatorium for inhalation treatment.

When an emanation apparatus is used, it is possible to collect the active deposit. The active deposit of rapid change is Radium A, B, C_1, C_2 and C′, and the active deposit of slow change, Radium D, E and F. The former have short disintegration periods and are the more active, the activity being inversely proportional to the period of disintegration.

Any substance exposed to the emanation becomes coated with the active deposit. The substances most often exposed are sodium chloride and lead foil, the former when a solution for intravenous injection is desired, the latter, for superficial application.

The active deposit decays rapidly when removed from the emanation, since it is not being constantly replaced by disintegrated emanation atoms. Its alpha ray activity is reduced to one-half its initial value in about fifteen minutes, but its gamma ray activity has a half period of one hour.

Therapy.—Radium therapy should be in the hands of skilled specialists. The determination of suitable dosage in each case requires training and judgment, and the best results are obtained only after a study of a series of cases. Only a trained man should be responsible for treatment by radium, as it is potent for harm as well as for good.

Technic.—The technic of filtration of radium by the use of suitable metallic or other screens, the length of time of application, and the amount of radium to be used vary with the pathologic condition. The radium salts and the emanation may be placed in any sealed container, preferably in glass. The quantity of radiation is roughly proportional to the amount of Radium C^1, C_1 or C_2 represented in the salt or in the emanation. The efficacy of the treatment is due to the beta and the gamma rays. Pure gamma rays are employed if the apparatus is surrounded by at least 3 mm. of lead. However, such infiltration is seldom employed in technical procedures against cancer or other serious lesions, because it is not usually necessary completely to filter out the beta rays; indeed, for certain lesions beta radiation is very useful, and filtration is arranged so as to provide a certain percentage of primary beta rays. At the present time there is a growing tendency, with the more resistant forms of tumors, to filter out as much of the beta rays as is practicable by the use of such filtration as 0.5 mm. of gold or the same thickness of platinum. Few radiologists use more than 1 mm. of lead, when lead is used at all, in actual treatment. Observation indicates that the action of radium rays on the malignant cell is complex, and the true nature of the changes produced is still obscure.

RADIUM AND ITS DISINTEGRATION PRODUCTS

Substance	Chemical Nature	Atomic Weight	Half Value Periods	Rays
Radium................	Metal	226	1,690 yrs.	Alpha
Radon (radium emanation).................	Inert gas	222	3.85 days	Alpha
Radium A.............	Solid nonmetal identical with polonium	218	3.0 min.	Alpha
Radium B.............	Identical with lead*	214	26.8 min.	Beta, Gamma
Radium C	Identical with bismuth	214	19.5 min.	99.97 Beta and Gamma
Radium C^1..	Identical with polonium	214	10^{-6} sec.	Alpha
Radium D...	Identical with lead*	210	16.5 yrs.	Beta and Gamma
Radium E...	Identical with bismuth	210	5.0 days	Beta, Gamma
Radium F[a]..	Identical with polonium	210	136 days	Alpha (and Gamma)
Radium Ω[b]..	Identical with lead	206		
Radium C...	Identical with bismuth	214	....	0.03 Alpha
Radium C^1............	Identical with thallium	210	1.4 min.	Beta
Radium Ω[c]..........	Identical with lead	210		

[a] Polonium.
[b] Lead.
[c] Hypothetical.
* Generally referred to as isotope.

Dosage.—Dosage is generally expressed in milligram hours or millicurie hours, the former being used for radium salts, the latter for the emanation; the two terms describe practically the same quantity. In ordinary use, however, there is a very slight discrepancy in their values, owing to the change in value of the emanation tube during the time of treatment. If the average value of the tube is used, this discrepancy is practically eliminated for any normal period of treatment. In a complete description of a treatment, the dosage, filtration, the distance from the lesion, and the type of applicator should be given. Confusion in the literature with regard to dosage is due to lack of care in the notation; the older writers based the dosage on the product of the period of application by the quantity of crystallized radium bromide ($RaBr_2+2H_2O$), which contains 53.6 per cent of radium element instead of on the product of the period of application by the quantity of radium element, producing an error of about + 40 per cent. The French describe dosage when emanation is used as the quantity of emanation destroyed. This they define as the difference between the intensity of radiation from the applicator at the beginning and at the end of the treatment.

In cases in which radium can be placed in direct contact with malignant tissue, screening is unimportant; but if the growth is deep seated or if normal tissue intervenes and a uniform irradiation is desired, the amount of radium, duration of exposure, screening and distance must be taken into account. Beta rays are comparatively easily absorbed, but the secondary beta rays given off by dense filters cause an erythematous reaction in the skin, and in sufficient exposure produce a local necrosis of the part.

The most efficient method of application of radium is to bury it within the substance of the tumor. Needles containing 10 to 12.5 mg. and made of steel alloy, gold, nickel-copper alloy or irridium-platinum alloy are used. The time of application depends on the number of needles and their relation to important structures.

The burying of glass capillary tubes containing the emanation, measuring from 0.5 to 1.0 millicuries each and placed within the tumor substance at the distance of about 1 cm. have been employed for these applications. However, to avoid undue reaction produced by the intense beta radiations from the unprotected glass implants when used in the treatment of malignancies of the mucous membrane, gold or other metal implants, containing radium emanation are now being employed. If the entire tumor cannot be radiated in this manner, it is best not to attempt this technic.

Distance Application.—One thousand milligram hours, applied as follows, is a safe dose and in some patients will produce a mild erythema: If 50 or 100 mg. of radium are used, contained in the universal silver tube applicator (walls 0.5 mm. thick; filtration 2 mm. lead and 2 mm. Para rubber at 2.5 cm. distance), the time of application is twenty and ten hours, respectively. The size of each skin area is 2.5 square centimeters. Distance may be maintained by the interposition of cork, gauze, felt, or wood. All regional skin within 2.5 cm. of the applicator should be protected with sheet rubber 2 mm. thick and sheet lead from 0.5 to 0.8 mm. thick.

Solutions of radium are said to exert certain effects in the body, particularly on the blood and to increase catabolic changes generally. The evidence is doubtful and for most of it confirmation is lacking.

The emanation following the administration of an emanation solution (such as that from radioactive water generators) is very soon lost from the body (a large portion also escapes during the process of drinking). Radium solutions may produce a condition of radioactivity in the body for a longer period than does radium emanation.

Results of Treatment in Pathologic Conditions.—Nearly all pathologic tissues are more sensitive than normal tissues. There is a wide variation, however, in the normal tissues; for instance, the ovary and other sexual organs are very sensitive; the eye and the nervous tissues are insensitive. In certain new growths, both benign and malignant, an arresting influence is exerted; of the malignant growths, the best results have been obtained with sarcomas, especially lymphosarcomas.

(*a*) *Intravenous and Oral Administration.*—Radium chloride solution and radon (radium emanation) contained in drinking water constitute the chief methods of oral administration; intravenously, radium chloride solution is generally used. Such evidence as is available on the use of solutions containing radium or radon (radium emanation) in the treatment of disease is in general not well controlled and is therefore of doubtful value. Certainly there is no basis for the use of radium or radon (radium emanation) in such conditions as anemia, habitual constipation, glycosuria, sexual impotency, glandular inefficiency, or for purposes of rejuvenation in general. It is noteworthy that many of the conditions in which radon is recommended for use are chronic conditions in which any new method of treatment may seem temporarily to be of benefit.

The daily administration of radon (radium emanation) has been reported to give beneficial results in various conditions, including infections, acute articular rheumatism, endocarditis, chronic rheumatism, neuritis, hypertension, thrombo-angiitis obliterans, and arthritis deformans. Many of the so-called emanators and activators on the market impart such small amounts of radon (radium emanation) to the water contained in them that their effects, if any, are no more than merely psychic.

Radium chloride solutions are given in doses of ten to fifty micrograms. While such dosage has not been proved to produce harmful results, the possibility of harm from long continued dosage must be considered.

From an examination of the available evidence it appears that the value of the internal use of radium solutions or of water containing radon, in chronic arthritis, gout, neuritis and high blood pressure is not demonstrated by controlled clinical evidence; that in spite of many years of trial, acceptable evidence has not become available, and until such evidence does become available the Council has decided not to accept generators for the production of water charged with radon or radium solutions intended for intravenous use.

(*b*) *Topical Administration.*—Observations on the treatment of myelogenous and lymphatic leukemia by radium show satisfactory remission. In some cases a marked degree of general improvement accompanies the reduction in the size of the spleen, and superficial glands, and a fall of the leukocyte count. In patients with a history of long duration, the results are not so striking. When the spleen is fibrous, the radium is less effective. In patients with severe anemia, radium exposures should be repeated with caution. Occasionally, a more acute anemia seems to be the result of radium exposures in cases of this type. Radium is applied for varying lengths of time over the spleen and superficial lymphatic enlargements. Usually, however, a total exposure of twenty-four hours over successive areas is sufficient at one time. This may be repeated at weekly intervals.

In menorrhagia and metrorrhagia, which are the usual concomitants of fibroid disease of the uterus, radium therapy is frequently of real value. It is accomplished best by intrauterine application, although the radium may be placed in the posterior vaginal fornix and supplemented with distance screening over the fundus. In young women, the dose should be controlled so that a premature menopause does not occur. A universal tube applicator containing 25 or 50 mg. of radium in the form of radium sulphate screened with 0.5 mm. of silver and 2 mm. of gum rubber, placed in the uterine cavity for fourteen hours, in most cases will bring on amenorrhea. The treatment may be repeated after six months, if necessary.

Lymphadenoma, lymphosarcoma, and mediastinal and abdominal growths of a sarcomatous nature are often reduced in size by the application of radium, with concomitant improvement in the general condition. Periosteal sarcomas following injury have been benefited by treatment with radium.

Palliation in cases of carcinoma generally follows the application of radium and apparently satisfactory results have been noted in early cases. It is desirable to employ radium as a prophylactic measure after cancer operation.

Radium treatment is of value in bringing on shrinking and fibrosis in the early stages of tuberculous adenitis.

Improvement has been noted in certain skin diseases when treated with radium rays, for example, eczema, lichenification, psoriasis, xanthoma mycosis, fungoides and fibroma. If only superficial layers are involved, short, intense exposures should be employed on three or four successive days; and if the deeper skin layers are involved, longer unscreened or lengthy screened exposures are needed.

Lupus vulgaris, when all other treatment has failed, is sometimes favorably influenced by radium.

The course of the disease in cavernous nevus is favorably influenced. The treatment is lengthy and tedious. Over-irradiation should be avoided, especially about the face, for it brings about scarring. Much care and experience are needed in order to obtain good results.

The removal of warts, papillomas and granulomas by radium is generally successful. If the exposure is timed properly, exfoliation occurs in from three to four weeks.

Good results have been reported in the treatment of war injuries, such as keloids, painful scars, fibrous adhesions and vicious cicatrices.

Moles, especially of the pigmented variety, should not be irradiated. Wide excision by a surgeon should be advised if the patient is insistent that something be done.

RADIUM BROMIDE. — Radii Bromidum. — $RaBr_2$. — The anhydrous radium salt of hydrobromic acid. — The market supply is usually a mixture of radium bromide and barium bromide and is sold on the basis of its radium content.

Actions, Uses and Dosage.—See preceding article, Radium and Radium Salts.

Pure anhydrous radium bromide, containing 58.6 per cent of radium (Ra), is a white or slightly brownish substance, soluble in water.

The presence of radium can qualitatively be demonstrated by electroscopic or by photographic methods. The quantitative determination of radium is carried out according to the method of Rutherford and Boltwood (Rutherford's "Radio-Active Substances and Their Radiations," Cambridge, 1913).

Radium Bromide-Radium Belge.—Supplied in the form of a mixture of radium bromide and barium bromide, containing 90 per cent or more of the radium salt. Sold on the basis of U. S. Bureau of Standards' measurement, with the radium purity (concentration) guaranteed by the Standard Chemical Company; it is also guaranteed that the gamma ray activity due to the presence of mesothorium, radiothorium. or substances other than radium and its derivatives does not exceed 0.2 per cent.

Manufactured by Radium Belge, Union Minière du Haut Katanga, Belgian Congo, Africa (Radium Chemical Company, Inc., New York, distributor).

RADIUM CARBONATE.—Radii Carbonas.—$RaCO_3$.—The anhydrous radium salt of carbonic acid.—The market supply is usually a mixture of radium carbonate and barium carbonate and is sold on the basis of its radium content.

Actions, Uses and Dosage.—See preceding article, Radium and Radium Salts.

Pure radium carbonate, containing 79 per cent of radium (Ra), is a white or slightly brownish salt, insoluble in water, decomposed by acids.

The presence of radium can be demonstrated qualitatively by electroscopic or by photographic methods. The quantitative determination of radium is carried out according to the method of Rutherford and Boltwood (Rutherford's "Radioactive Substances and Their Radiations").

Radium Carbonate-Radium Belge.—Supplied in the form of a mixture of radium carbonate and barium carbonate, containing 90 per cent or more of the radium salt. Sold on the basis of U. S. Bureau of Standards' measurement, with the radium purity (concentration) guaranteed by the Standard Chemical Company; it is also guaranteed that the gamma ray activity due to the presence of mesothorium, radiothorium, or substances other than radium and its derivatives does not exceed 0.2 per cent.

Manufactured by Radium Belge, Union Minière du Haut Katanga, Africa (Radium Chemical Co., Inc., New York, distributor).

RADIUM CHLORIDE. — Radii Chloridum.—$RaCl_2$.—The anhydrous radium salt of hydrochloric acid. The market supply is usually a mixture of radium chloride and barium chloride and is sold on the basis of its radium content.

Actions, Uses and Dosage.—See preceding article, Radium and Radium Salts.

Pure anhydrous radium chloride, containing 76.1 per cent radium (Ra), is a white or slightly brownish substance, soluble in water.

The presence of radium can qualitatively be demonstrated by electroscopic or by photographic methods. The quantitative determination of radium is carried out according to the method of Rutherford and Boltwood (Rutherford's "Radioactive Substances and Their Radiations").

RADIUM SULPHATE. — Radii Sulphas. — $RaSO_4$. — The anhydrous radium salt of sulphuric acid. The market supply is usually a mixture of radium sulphate and barium sulphate and is sold on the basis of its radium content.

Actions, Uses and Dosage.—See preceding article, Radium and Radium Salts.

Pure radium sulphate, containing 70.2 per cent radium (Ra), is a white substance insoluble in water and dilute acids.

The presence of radium can be demonstrated qualitatively by electroscopic or by photographic methods. The quantitative determination of radium is carried out according to the method of Rutherford and Boltwood (Rutherford's "Radioactive Substances and Their Radiations").

Radium Sulphate-Radium Belge.—Supplied in the form of a mixture of radium sulphate and barium sulphate, containing 90 per cent or more of the radium salt. Sold on the basis of U. S. Bureau of Standards' measurement, with the radium purity (concentration) guaranteed by the Standard Chemical Company; it is also guaranteed that the gamma ray activity due to the presence of mesothorium, radiothorium, or substances other than radium and its derivatives does not exceed 0.2 per cent.

Manufactured by Radium Belge, Union Minière du Haut Katanga, Africa (Radium Chemical Co., Inc., New York, distributor).

RADON.—Radium Emanation.—The radioactive gas which results when radium atoms transmute by the loss of the so-called alpha particle, admixed with inert gases. It is supplied in sealed glass, gold or platinum containers and is sold on the basis of the amount of emanation in terms of millicuries present at the time of sale.

Actions and Uses.—The therapeutic applications of radon are identical with those of radium salts. However, while the activity of radium salt is practically constant, that of radon decreases rapidly (see preceding article, Radium and Radium Salts). On the other hand, the smaller bulk of radon preparations as compared with radium preparations with similar gamma ray activity makes the use of radon advantageous under certain circumstances.

Dosage.—See preceding article, Radium and Radium Salts. Therapeutically the penetrating radiation from one millicurie of radium is of the same nature and intensity as that from one milligram of radium, but the radiation available from a tube of radon is greater than that from a tube containing the same number of milligrams of radium. The intensity of radiation from an initial millicurie does, however, not remain practically constant as in the case of radium because of the rapid decay of the emanation (about three-fourths per cent per hour). Because of its rapid decay, radon in the form of "seeds" may be implanted into tumor masses and the tiny glass, gold or platinum implants allowed to remain in the mass; if the quantity of radon is suitably chosen, the necessary dosage is produced during the decay of the radon.

Radon-Radium Emanation Corporation.—A brand of radon-N. N. R. It is supplied, according to the physician's specification, in sealed containers of brass, copper, silver, gold, platinum or rubber, or combination of these materials. Each container is accompanied by a statement of the amount of radon in terms of millicuries contained in it at the time of sale.

Manufactured by the Radium Emanation Corporation, New York. No U. S. patent. U. S. trademark 183,890 (The Council recognizes the trademark as a design only; it does not recognize the right of the Radium Emanation Corporation to the exclusive use of the name radon.)

Radon-Radium Emanation Corporation is obtained by removing the radon produced in a solution of a radium salt. The radon is removed from the solution by a system of mercury pumps together with other gases formed by the decomposition. The extraneous gases are for the most part removed by chemical means. The residual gas with the emanation is forced into the desired container.

To determine the radon content of a sealed container it is compared after equilibrium is attained by determination of the gamma ray activity with a tube of radium salt standardized by the U. S. Bureau of Standards. The tubes are shipped in lead lined containers.

Radon-Radon Co., Inc.—A brand of radon-N. N. R. It is supplied in the form of implants (minute glass or gold tubes suitable for embedding in tumors) and in the form of larger tubes; strength and screenage according to the physician's specifications. Radon-Radon Co., Inc., is sold on the basis of its gamma ray activity, as determined by comparison with a radium standard.

Manufactured by the Radon Co., Inc., New York. No U. S. patent or trademark.

RESORCIN COMPOUNDS

CAPROKOL.—Hexylresorcinol-S. & D.—Normal hexylresorcinol, $C_6H_3(OH)_2(C_6H_{13})$, containing not more than 5 per cent of the intermediate product, hexylylresorcinol.

Actions and Uses.—Caprokol possesses marked germicidal properties, is stated to have a phenol coefficient of over 70 and to be relatively nontoxic when administered by mouth. It is excreted by the kidneys, being largely decomposed but imparting definite germicidal properties to the urine.

Experiments have been reported which showed that when normal urine inoculated with *Bacillus coli* and *Staphylococcus albus* from cases of pyelitis was treated with caprokol in the proportion of 1 in 10,000 the organisms were destroyed both in acid and alkaline urine. Caprokol was not found toxic to rabbits in doses of 1 to 2.5 Gm. nor in daily doses of 0.5 Gm. given over a period of three weeks. Doses of from 1 to 7 Gm. in olive oil given to normal men in repeated doses produced no important toxic effects. Administration of caprokol to normal individuals in doses of 0.25 to 0.5 Gm. three times a day caused secretion of urine which killed *Bacillus coli* and *Staphylococcus albus*, but the effects were not constant. The drug seems to offer the possibility of obtaining a continuous flow of bactericidal urine.

Caprokol is proposed for the treatment of urinary infections. The drug appears to be efficient against infections due to *Streptococcus anhemolyticus* and *Bacillus pyocyaneus*, but to be less efficient in the treatment of infections due to *Bacillus coli*.

Dosage.—Internally, from 0.15 to 0.6 Gm. three times a day. Caprokol is supplied for internal use in the form of an olive oil solution in gelatin capsules.

Manufactured by Sharp & Dohme, Baltimore. U. S. patent applied for; U. S. trademark 191,984.

Capsules Caprokol (Hexylresorcinol-S. & D.), 0.15 Gm.: Each capsule contains 0.15 Gm. hexylresorcinol-S. & D. dissolved in olive oil 0.45 Gm.

Caprokol (Hexylresorcinol-S. & D.) 2½ per cent. Solution in Olive Oil.

Hexylresorcinol Solution S. T. 37: A solution of hexylresorcinol-S. & D., 1 part, in a liquid composed of glycerin 30 per cent and water 70 per cent, 1,000 parts.

Caprokol is a heavy viscous, pale yellow liquid, which solidifies on standing at room temperature. It boils at 178 C. under 8 mm. pressure; the crystals (from the distillate) melt at not lower than 58 C.

It is very slightly soluble in water (1 part in 2,000 parts of water) but readily soluble in alcohol, ether, chloroform, benzene and vegetable oils. It has a slightly pungent odor, a sharp astringent taste, and produces a sense of numbness when placed on the tongue.

Add 1 cc. of nitric acid to 1 cc. of saturated aqueous solution of caprokol: a bright red color forms. Add 1 cc. of bromine water to 1 cc. of an aqueous solution of caprokol: a yellow flocculent precipitate forms; on addition of 2 cc. of ammonia water the precipitate dissolves, leaving a canary yellow solution. Shake about 1 Gm. of caprokol with 50 cc. of water, withdraw the aqueous layer and add three drops of ferric chloride solution: no blue color forms (*resorcinol*).

Incinerate about 2 Gm. of caprokol accurately weighed: the ash weighs not more than 0.001 Gm.

To 5 cc. of an alcoholic solution of caprokol 1 per cent, add three drops of ferric chloride solution; the color produced should not be greater than that formed by the addition of three drops of ferric chloride solution to 5 cc. of an alcoholic solution containing pure hexylresorcinol (made by redistilling at 178 C. under pressure of 8 mm. and melting at 57 to 60 C.) 0.95 per cent. and hexylylreorcinol 0.05 per cent.

RESORCINOL MONOACETATE. — Resorcin Acetate, *m*-Hydroxyphenyl Acetate. — *m*-Acetyloxyphenol $C_6H_4(OH).(OOCCH_3)$. The monoacetic ester of resorcinol.

Actions and Uses.—The action of resorcinol monoacetate is similar to that of resorcinol, but milder and more lasting because of the gradual liberation of resorcinol.

Resorcinol monoacetate is used in the treatment of acne, sycosis, chilblains, and particularly in the treatment of alopecia and seborrhea.

Dosage.—Resorcinol monoacetate is applied in ointments of from 5 to 20 per cent and in acetone solution. For scalp lotions, alcoholic solutions of from 3 to 5 per cent are used.

Resorcinol monoacetate is a viscous, lemon yellow liquid, boiling under ordinary pressure at 283 C. with decomposition. It is soluble in alcohol, acetone and most organic solvents; sparingly soluble in water. It has a faint characteristic odor and burning taste. Resorcinol monoacetate, at a pressure of 10 mm., distils completely between 150 and 153 C.

Dissolve 10 cc. resorcinol monoacetate in 20 cc. benzene and shake with 100 cc. o f distilled water containing methyl orange solution: not more than 0.5 cc. tenth-normal alkali is required to neutralize the free acidity.

Euresol.—A brand of resorcinol monoacetate-N. N. R.

Manufactured by E. Bilhuber, Inc., New York. No U. S. patent. U. S. trademark 88,894.

Euresol pro Capillis: Euresol perfumed to render it suitable for scalp lotions.

Resorcinol Monoacetate-Eastman Kodak Co.—A brand of resorcinol monoacetate-N. N. R.

Manufactured by the Eastman Kodak Co., Rochester, N. Y. No U. S. patent or trademark.

RHUS PREPARATIONS

IVYOL.—Poison Ivy Extract-Mulford.—A solution in olive oil of an irritant or vesicant oil extracted from the fresh leaves of poison ivy (*Rhus toxicodendron*).

Actions and Uses.—Ivyol is used to relieve the symptoms of the dermatitis produced through contact with poison ivy.

Dosage.—In cases of average susceptibility, 0.7 cc. at daily intervals for four doses or until relieved. In cases of unusual susceptibility, from 0.2 to 0.35 cc., increased or not as indicated.

Manufactured by H. K. Mulford Company, Philadelphia. U. S. patent 1,559,340 (Oct. 27, 1925; expires, 1942). U. S. trademark applied for.

Hypo Units Ivyol: Collapsible syringe containers, each containing 0.7 cc. of ivyol.

The fresh leaves of *Rhus toxicodendron* are extracted with purified petroleum benzin. The resulting extract is filtered through paper and decolorized by agitation with fullers' earth. The decolorized extract is concentrated in vacuo to one-tenth its original volume; the concentrated extract is allowed to evaporate spontaneously to dryness; and the residue dissolved in sterile olive oil in the proportion of one part of the extract to 1,000 parts of oil, and 2 per cent of camphor added as a preservative.

POISON IVY EXTRACT-LEDERLE (IN ALMOND OIL).—A solution in almond oil of a substance extracted from the fresh leaves of poison ivy (*Rhus toxicodendron*).

Actions and Uses.—Poison ivy extract-Lederle (in almond oil) is used to relieve the symptoms of the dermatitis produced through contact with *Rhus toxicodendron.*

Dosage.—From 0.5 to 1 cc. injected intramuscularly at intervals of from twenty-four to forty-eight hours.

Manufactured by the Lederle Antitoxin Laboratories, New York. No U. S. patent or trademark.

Poison Ivy Extract-Lederle (in Almond Oil) 1 cc.: Syringes containing 1 cc. of poison ivy extract-Lederle (in almond oil).

Freshly gathered mature leaves of *Rhus toxicodendron* are macerated with acetone. The resulting extract is decolorized and dehydrated and then concentrated until the content of solid matter becomes 20 per cent. Five parts of this liquid are added to 95 parts of sterile almond oil containing 1 per cent of chlorbutanol and this liquid is filtered.

POISON OAK EXTRACT-LEDERLE (IN ALMOND OIL).—A solution in almond oil of a substance extracted from the fresh leaves of poison oak *(Rhus diversiloba).*

Actions and Uses.—Poison oak extract-Lederle (in almond oil) is used to relieve the symptoms of the dermatitis produced through contact with poison oak.

Dosage.—From 0.5 to 1 cc. injected intramuscularly at intervals of from twenty-four to forty-eight hours.

Manufactured by the Lederle Antitoxin Laboratories, New York. No U. S. patent or trademark.

Poison Oak Extract-Lederle (in Almond Oil) 1 cc.: Syringes containing 1 cc. of poison oak extract-Lederle (in almond oil).

Freshly gathered mature leaves of *Rhus diversiloba* are macerated with acetone. The resulting extract is decolorized and dehydrated and then concentrated until the content of solid matter becomes 20 per cent. Five parts of this liquid are added to 95 parts of sterile almond oil containing 1 per cent of chlorbutanol and this liquid is filtered.

RHUS TOX. ANTIGEN-STRICKLER.—A solution of a substance extracted from the fresh leaves of *Rhus toxicodendron;* it contains 0.4 Gm. of procaine hydrochloride in each 100 cc.

Actions and Uses.—Rhus tox. antigen-Strickler is used to determine sensitiveness to *Rhus toxicodendron,* and to relieve the symptoms of the dermatitis produced through contact with the plant.

Dosage.—To determine sensitiveness to *Rhus toxicodendron,* 0.1 cc. of rhus tox. dermal test is injected intradermally. For treatment, three doses of from 0.5 to 1 cc. injected intramuscularly are given at twenty-four hour intervals.

Manufactured by the American Chemical Laboratories, Philadelphia. No U. S. patent or trademark.

Rhus Tox. Antigen-Strickler: Packages of four 1 cc. vials, each cc. containing 0.0125 Gm. of substance dissolved in 40 per cent alcohol.

Rhus Tox. Dermal Test: Packages of a 1 cc. vial, each cc. containing 0.005 Gm. of substance dissolved in a menstruum composed of dextrose, 15 per cent; alcohol, 10 per cent, and water, 75 per cent (accompanied by a vial of rhus venenata dermal test).

Freshly gathered leaves of *Rhus toxicodendron* are extracted with absolute alcohol; the alcohol is removed, the residue is extracted with chloroform to remove the chlorophyll, and then treated with zinc sulphate; sodium phosphate is then added to precipitate the zinc as zinc phosphate; the precipitate is then collected and dried. The precipitate is extracted successively with ether, amyl alcohol and dimethyl carbonol in an extraction apparatus, the extractions evaporated and the residual extract dried at a low temperature.

RHUS VENENATA ANTIGEN-STRICKLER.—A solution of a substance extracted from the fresh leaves of *Rhus venenata;* it contains 0.4 Gm. of procaine hydrochloride in each 100 cc.

Actions and Uses.—Rhus venenata antigen-Strickler is used to determine sensitiveness to *Rhus venenata,* and to relieve the symptoms of the dermatitis produced through contact with the plant.

Dosage.—To determine sensitiveness to *Rhus venenata,* 0.1 cc. of rhus venenata dermal test is injected intradermally. For treatment, three doses of from 0.5 to 1 cc. injected intramuscularly are given at twenty-four hour intervals.

Manufactured by the American Chemical Laboratories, Philadelphia. No U. S. patent or trademark.

Rhus Venenata Antigen-Strickler: Packages of four 1 cc. vials, each cc. containing 0.0125 Gm. of substance dissolved in 40 per cent alcohol.

Rhus Venenata Dermal Test: Packages of a 1 cc. vial, each cc. containing 0.005 Gm. of substance dissolved in a menstruum composed of dextrose, 15 per cent; alcohol, 10 per cent, and water, 75 per cent (accompanied by a vial of rhus tox. dermal test).

Freshly gathered leaves of *Rhus venenata* are extracted with absolute alcohol; the alcohol is removed, the residue is extracted with chloroform to remove the chlorophyll and then treated with zinc sulphate; sodium phosphate is then added to precipitate the zinc as zinc phosphate; the precipitate is then collected and dried. The precipitate is extracted successively with ether, amyl alcohol and dimethylethyl carbonol in an extraction apparatus, the extractions evaporated and the residual extract dried at a low temperature.

SALICYLIC ACID COMPOUNDS

To avoid the disagreeable taste and gastric symptoms of salicylates, esters and similar compounds have been introduced, which are more or less insoluble, so that the salicyl radical is liberated only in the intestine or after absorption into the blood. These compounds have little or no direct action on the stomach. Notwithstanding this, nausea and vomiting are frequently induced, probably owing to action on the central nervous system. In practice, these compounds are not superior to sodium salicylate, which does not produce direct gastric irritation when properly guarded by a bicarbonate.

The taste of these compounds is much less objectionable than that of the simpler salicylate salts, but this advantage scarcely balances their high cost.

The alkyl esters (methyl salicylate type) are absorbed readily from the skin and are therefore better for external use than simpler salicylates.

The acyl derivatives (acetylsalicylic acid type) posssess a higher analgesic and antipyretic action and have therefore a special field.

The salols contain active phenols which adapt them to intestinal antisepsis.

Salicylic acid compounds may be arranged under four types:

1. Compounds formed by replacing the hydrogen (H) of the hydroxyl group (OH) in salicylic acid, by acyl radicals. To this type belong acetylsalicylic acid (aspirin) $C_6H_4O.(COCH_3).COOH$ and novaspirin.

2. Compounds formed by replacing the hydrogen (H) of the carboxyl group (COOH) in salicylic acid by alkyl radicals; methyl salicylate, $C_6H_4.OH.COO(CH_3)$, and the corresponding ethyl salicylite, methoxymethyl salicylite (mesotan), monoglycol salicylate (spirosal), and methyl benzoyl salicylate (benzosalin). Of these, ethyl salicylate, mesotan and spirosal are described in N. N. R.

3. Compounds formed by replacing the hydrogen (H) of the carboxyl group (COOH) in salicylic acid by phenol radicals: phenyl salicylate (salol), $C_6H_4.OH.COO(C_6H_5)$, and the corresponding betanaphthyl salicylate, and acetparamidophenyl salicylate (phenetsal). Of these, betanaphthyl salicylate and phenetsal are described in N. N. R.

4. Salicylic compounds in which the salicylic action is subordinate. Those described in N. N. R. are: salipyrin, mercuric salicylate and santyl.

SALICYL IN VARIOUS DERIVATIVES, IN TERMS OF SALICYLIC ACID AND SODIUM SALICYLATE

100 parts of sodium salicylate = 85.6 parts of salicylic acid = 100 of sodium salicylate.

100 parts of methyl salicylate = 90.7 parts of salicylic acid = 106 of sodium salicylate.

100 parts of acetylsalicylic acid = 77 parts of salicylic acid = 89 of sodium salicylate.

100 parts of salicyl-salicylate = 106.2 parts of salicylic acid = 124 of sodium salicylate.

Acid Derivatives of Salicylic Acid (Acetylsalicylic Acid Type)

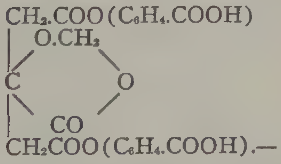
These are employed in rheumatic conditions, and especially as analgesics and antipyretics in colds, neuralgias, etc. Their analgesic effects surpass those of sodium salicylate, with less danger of local irritation. The promiscuous use of acetylsalicylic acid (aspirin) by the laity, especially for the relief of headache, has frequently led to cases of rather severe poisoning, the chief symptoms being edema of the lips, tongue, eyelids, nose or of the entire face; also urticarial rashes, vertigo, nausea and sometimes cyanosis. Some persons are especially susceptible to acetylsalicylic acid and these symptoms are usually ascribed to an idiosyncrasy.

ACETYLSALICYLIC ACID.—For description see the U. S. Pharmacopeia and Useful Drugs under Acidum Acetylsalicylicum.

Actions and Uses.—See preceding article, Acid Derivatives of Salicylic Acid (Acetylsalicylic Acid Type).

Dosage.—From 0.3 to 1 Gm. (5 to 15 grains), repeated once in three hours until symptoms of salicylism (ringing in the ears, etc.) are noted. It may be administered in the form of a powder, wafers, or capsules. If prescribed as a powder, this may be administered by dissolving it in sweetened water, or by placing it on the tongue, and taking a swallow of water. The powder should be dispensed in wax paper.

NOVASPIRIN. — Salicitrin. — Methylene-Citrylsalicylic Acid.



A compound of anhydromethylenecitric acid and salicylic acid.

Actions and Uses.—See preceding article, Acid Derivatives of Salicylic Acid (Acetylsalicylic Acid Type).

Dosage.—1 Gm. (15 grains), several times daily.

Manufactured by Winthrop Chemical Company, Inc., New York City. U. S. patent 858,142 (June 25, 1907; expired). U. S. trademark 62,613.

Novaspirin Tablets, 5 grains.

Novaspirin is a grayish-white odorless, crystalline powder, permanent in the air, having a faint acidulous taste. It is almost insoluble in water; soluble in alcohol; less soluble in ether or chloroform. On heating novaspirin with caustic alkalis, salicylate is formed, and on adding diluted acid to the alkaline solution, crystals of salicylic acid are separated. On long standing in the presence of water or more quickly with alkalis, novaspirin is split into its components. When heated in a dry test tube novaspirin melts, and at higher temperatures formaldehyde and salicylic acid are liberated. The salicylic acid sublimes and is deposited on the cooler portions of the tube. Novaspirin when decomposed yields 62 per cent of salicylic acid. After drying over sulphuric acid to constant weight, novaspirin melts at from 153 to 154 C. A saturated, aqueous solution of novaspirin (prepared without heat) does not produce a violet color with ferric chloride solution.

Incinerate 1 Gm. of novaspirin; not more than 0.1 per cent of ash remains.

Dry 1 Gm. of novaspirin over sulphuric acid; the loss in weight is not more than 5 per cent.

Alkyl Derivatives of Salicylic Acid (Methyl-Salicylate Type)

These act somewhat more slowly, but otherwise as efficiently as sodium salicylate. They are for the most part saponified in the intestines, but some may be absorbed unchanged. They have not the disagreeable taste, but frequently they cause somewhat more local irritation. They are also quite well absorbed from the skin, and may, therefore, be applied externally, usually dissolved in olive oil. Methyl salicylate is official in the U. S. Pharmacopeia.

ETHYL SALICYLATE.—Aethylis Salicylas.—$C_6H_4.OH.C.O.O.(C_2H_5)$.—The salicylic acid ester of ethyl alcohol analogous to methyl salicylate (oil of wintergreen).

Actions and Uses.—Ethyl salicylate has the same action as methyl salicylate, but is said to be less irritant and less toxic.

Dosage.—From 0.3 to 0.6 cc. (5 to 10 minims) three or four times a day.

It is a transparent, colorless, volatile liquid, possessing a pleasant characteristic odor and taste. Its specific gravity is 1.132 at 20 C. and it boils at from 230 to 232 C. It is insoluble in water, but soluble in alcohol.

Ethyl Salicylate-Merck.—A brand of ethyl salicylate-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.

Sal-Ethyl.—A brand of ethyl salicylate-N. N. R.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent. U. S. trademark 92,115.

Sal-Ethyl Capsules, 5 minims.

MESOTAN.—Salmester.—$C_6H_4.OH.CO.O.(CH_2.O.CH_3)$.—Methyloxymethyl salicylate, an ester of salicylic acid, analogous to methyl salicylate.

Actions and Uses.—Mesotan is an active counterirritant, used especially in rheumatic conditions, similarly to the local application of methyl salicylate. It is more irritant than the latter, and lacks its odor. It is absorbed from the skin, but its action is predominantly local, relieving pain and swelling. It is not an efficient means for producing the systemic actions of salicylates.

Dosage.—For application mesotan is diluted with 1 to 4 parts of olive oil or cotton seed oil, and painted over the affected area usually twice daily. Friction should not be used, and dressings, if any are necessary, should be light and permeable. The site of application should be changed, if possible, after each treatment; or the area may be rested for two days after four days of treatment.

Manufactured by The Bayer Co., Rensselaer, N. Y. (Winthrop Chemical Co., Inc., New York, distributor). U. S. patent No. 706,018 (Aug. 5, 1902; expired). U. S. trademark no. 39,017.

Mesotan is a clear, yellowish, faintly aromatic, oily fluid, specific gravity 1.2 at 15 C. and boiling at about 162 C. It is but slightly soluble in water, but readily soluble in the usual organic solvents and miscible with oils in all proportions. Above 100 C. it is decomposed, yielding salicylic acid, formaldehyde and methyl alcohol, and it is likewise decomposed to a certain extent by moisture in the air.

The aqueous solution of mesotan gives a violet color with ferric chloride and, after heating or exposure to moisture, it responds to the usual tests for formaldehyde. Concentrated sulphuric acid colors it red.

Mesotan should be kept in a cool place and preserved dry in well-stoppered bottles.

SPIROSAL. — Monoglycol-Salicylate. — Glysal. — $C_6H_4OH.CO.O.(CH_2.CH_2.OH)$.—The salicylic acid ester of monoglycol.

Actions and Uses.—When spirosal is applied to the skin from about one-fifth to one-sixth of the amount used is absorbed. Usually it causes very little irritation even when rubbed in thoroughly.

Dosage.—It is used undiluted or mixed with from 2 to 3 parts of alcohol or in a mixture with olive oil, 1 to 8, or in ointments with equal parts by weight of petroleum or lard.

Manufactured by The Bayer Company, Rensselaer, N. Y. Winthrop Chemical Company, Inc., distributor. U. S. patent 794,982 (July 18, 1905; expired). U. S. trademark 62,856.

Spirosal is an almost odorless and colorless oily fluid, with a boiling-point of from 169 to 170 C. at 12 mm. pressure. It is easily soluble in alcohol, ether, chloroform and benzol and soluble in about 110 parts of water and 8 parts of olive oil.

When 0.5 Gm. spirosal is saponified with 5 cc. sodium hydroxide solution by slight warming, the clear fluid diluted with water and acidified with dilute sulphuric acid, fine crystalline needles of salicylic acid are formed, which, after being extracted with ether and the latter then evaporated, can be identified by the melting point and ferric chloride reaction. The saturated aqueous solution obtained by shaking 1 cc. of spirosal with 50 cc. of water gives a filtrate, which becomes intensely violet on addition of ferric chloride, but should not be changed by barium nitrate or silver nitrate solution. Five-tenths Gm. of spirosal when added to 2 cc. of concentrated sulphuric acid should give a light yellow and not a brownish color; 0.3 Gm., if incinerated on platinum foil, should not leave any weighable residue.

Phenol Derivatives of Salicylic Acid (Salol Type)

Phenol derivatives of salicylic acid of the salol type are used mainly as intestinal antiseptics. Phenyl salicylate (salol) is official.

BETANAPHTHYL SALICYLATE.—See Naphthol Compounds.

PHENETSAL.—See Phenetidin Derivatives.

Salicylic Compounds in Which the Salicylate Action Is Subordinate

MERCURIC SALICYLATE.—See Mercuric Compounds.

SALIPYRIN.—See Pyrazolon Derivatives.

SANTYL.—See Sandalwood Oil Derivatives.

SANDALWOOD OIL DERIVATIVES

The oil of sandalwood is eliminated chiefly by the kidneys and is a fairly effective urinary antiseptic, although it is inferior to methenamine in acid urines. It is used particularly in subacute or chronic urethritis and cystitis. The oil, at times, is disturbing to the stomach, and medicinal doses may cause irritation of the bladder with dysuria and pain in the kidney region and urethra.

The new derivatives of santal oil are generally less irritating than the oil itself.

ARHEOL.—Santalol.—A sesquiterpenic alcohol, the chief constituent of sandalwood oil. Arheol contains not less than 98 per cent of santalol.

Actions and Uses.—The action of arheol is the same as that of sandalwood oil. It is used in urethritis, cystitis and vesical catarrh, especially from gonorrhea.

Dosage.—From 0.4 to 0.6 Gm. (6 to 10 grains). Arheol is marketed only in capsules containing 0.2 Gm. (3 grains) of which from 9 to 12 capsules are to be taken daily.

Manufactured by P. Astier Laboratories, Paris and New York (Gallia Laboratories, Inc., New York, distributors). No U. S. patent. U. S. trademark 72,513.

Arheol Capsules: Arheol, 0.2 Gm. (3 grains).

Arheol is a colorless, oily liquid; specific gravity about 0.968 at 15 C. It is insoluble in water but soluble in alcohol. It boils under 11 Mm. pressure at 169 C., and under ordinary pressure at about 300 C.

SANTYL.—Santalolis Salicylas.—Salicylic Ester of Santalol.—Santalyl Salicylate.—$C_6H_4OH.COO(C_{15}H_{23})$.—The salicylic acid ester of santalol.

Actions and Uses.—It is said that santyl passes the stomach unchanged, but is slowly split up in the intestines into its constituents, santalol and salicylic acid. Santyl is claimed to have the same actions as sandalwood oil, except that because of the slow liberation of santalol, it produces less irritation of the gastro-intestinal tract or of the kidneys and urinary passages, and no unpleasant odor or eructations.

It is claimed to be useful in the same manner as santal oil for gonorrheal urethritis.

Dosage.—1.5 cc. (24 minims) usually given in 4 capsules of 0.4 cc. (6 minims) each, three times a day. It is incompatible with alkalis and with the usual incompatibles of the sandalwood oil and of salicylates.

Manufactured by E. Bilhuber, Inc., New York. U. S. patent 862,858 (Aug. 6, 1907; expired) by license from The Chemical Foundation, Inc. U. S. trademark 61,255.

Santyl Capsules, 6 minims.

According to the German patent the neutral esters of sandalwood oil are produced by heating the oil with the respective acid anhydrides and subsequent purification of the product.

Santyl is a yellowish oil with only a faint balsamic odor and taste; specific gravity, 1.07 at 15 C.; it boils under 20 Mm. pressure at 121 C. to 126.6 C., with partial decomposition. It is insoluble in water, but soluble in about 10 parts of alcohol.

Santyl should possess the physical constants given above. On saponification with alcoholic sodium hydroxide it should yield approximately 40 per cent of salicylic acid and 60 per cent of santalol.

SCOPOLAMINE

The scopolamine (or hyoscine) of the U. S. P. consists of the levorotatory compound. The optically inactive compound has the same effect on the central nervous system as has the official or levorotatory compound; it has but one-half the activity on peripheral organs (eye, heart, secreting glands). The absence of the latter action may in some cases be desirable, and in such cases there may be advantages in using the optically inactive compound; this has been introduced under the name "euscopol."

SCOPOLAMINE STABLE-ROCHE.—Scopomannit.—An aqueous solution of pure scopolamine hydrobromide, protected against decomposition by the addition of 10 per cent of mannite, supplied in ampules, each containing 1.2 cc. (1 cc. contains 0.0003 Gm. of scopolamine hydrobromide).

Actions, Uses and Dosage.—The same as those of scopolamine hydrobromide, U. S. P. (See Useful Drugs.)

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J.). No U. S. patent. German patent 266,415. U. S. trademark 103,288 and 103,289.

Scopolamine stable-Roche is prepared from freshly manufactured scopolamine hydrobromide having an optical activity of —26.0° for the sodium line (determined in an aqueous solution containing the equivalent of 4.5 Gm. of anhydrous scopolamine hydrobromide in 100 cc. at a temperature of 15 C. in a 100 millimeter tube) and a melting point of 195 C. by dissolving in an aqueous 10 per cent solution of mannite.

That scopolamine stable-Roche contains all of its scopolamine in an undecomposed state may be determined by comparing its action with that of a freshly prepared solution of scopolamine hydrobromide. For this purpose the manufacturers recommend the method of Langer, in which the frog heart is stopped by muscarine, or, better, by pilocarpine, and the systolic beat is reestablished by the addition of scopolamine, which is antagonistic to both muscarine and pilocarpine.

SERUMS AND VACCINES

Under this heading are described in the following pages agents of a complex biologic nature which are used in the treatment and diagnosis of disease and which depend for their action on various phases and relations of immunity.

Federal Regulations.—The urgent need for control of many of these potent and, in some cases, dangerous products has been partly met by a federal law entitled "An act to regulate the sale of viruses, serums, toxins, and analogous products in the District of Columbia, to regulate interstate traffic in said articles and for other purposes." Under this law the importation, exportation or interstate sale of these products is expressly forbidden unless the manufacturer hold a license from the Secretary of the Treasury.

It is to be noted that the protection of the federal law is of avail only in the case of prophylactic and therapeutic preparations which are shipped for interstate sale. Only products which are licensed for import, export or interstate sale and which have not been found to conflict with the rules of the Council will be found listed here. In purchasing the products for use, preference should be given to those which have been kept continually at a low temperature.

Dating of Biologic Products.—The federal law requires that each package of biologic products be marked with an expiration date, "the date beyond which the contents cannot be expected beyond reasonable doubt to yield their specific result." The regulations framed under this law, as outlined below, prescribe for each class of product how long after date of manufacture or issue this expiration date may be; but the temperature at which the product is kept after leaving the manufacturer's hands cannot be controlled. The temperature on the shelves of the supply house or drug store during storage is fully as important as the time of such storage, and physicians would do well to secure their biologic products from stocks which are shown by actual continuous thermometer records to have been kept in cold storage. This is particularly applicable to the more rapidly deteriorating products, such as vaccine virus, rabies vaccine, diphtheria toxin-antitoxin mixture, and antimeningococcic serum.

Official potency standards have been established, or official potency tests are made at the Hygienic Laboratory prior to the release of each lot, for the following products: diphtheria antitoxin, tetanus antitoxin, scarlet fever streptococcus antitoxin, perfringens antitoxin, diphtheria toxin-antitoxin mixture, antidysenteric serum, antimeningococcic serum, bacterial vaccines prepared from paratyphoid bacillus A, paratyphoid bacillus B, and typhoid bacillus, diphtheria toxin for the Schick test and scarlet fever streptococcus toxin for the Dick test and for immunization. For these products the dating of each lot is based on the last test for potency, that is, the date of manufacture is taken as the last date of satisfactorily passing a potency test. For all other biologic products, the testing for potency is on a less satisfactory basis, and the date of manufacture is counted as the date of removal from the animal in case of animal products, or the date of cessation of growth in the case of other products. For the purpose of determining the expiration date, the date of issue may be used instead of the date of manufacture, provided the product has been kept between manufacture and issue not longer than the following periods, at the corresponding temperature: twenty-four months constantly below 0 C.; or twelve months constantly below 5 C., or six months constantly below 10 C.; or three months constantly below 15 C.

Added Preservatives.—The preservation of serums, vaccines, etc., requires the addition of some antiseptic. In the preservation of serums which are used in larger volumes, the amount and character of the preservative are more important matters. The most commonly used antiseptics are cresol (0.4 per cent), phenol (0.5 per cent), and glycerin.

Immunity Reactions.—Immunity, in its broadest medical sense, means resistance to disease or harm. To attempt a more precise definition would give emphasis to certain theories or parts of the subject to the exclusion of others. The science of immunity, however, is chiefly concerned with the specific reactions which occur after a preparation containing the micro-organisms of an infectious disease or a complex substance similar to the products of micro-organisms is introduced within the body. In general, these reactions are specific; for instance, diphtheria toxin stimulates the body to produce an antitoxin which combines with no other toxin save that produced by the diphtheria bacillus.

The reactions of immunity may act either to prevent disease or to cure it, or to distinguish one disease from another. Accordingly, the products enumerated in this section may be used in prophylaxis, in treatment, or in diagnosis. Immunity may be natural to the individual or it may be acquired. That which is called into play by the use of these products is, of course, acquired immunity, and artificial at that; i. e., not conferred by a casual attack of the disease in question.

There is a further classification of acquired immunity into passive and active forms. In active immunity, the agents which actually perform the protective work are created within the body. In passive immunity, these agents are introduced ready formed from without. This gives us a basis for the classification of the therapeutic products. Those of the first class, the serums, and the antitoxins, which are derived from the serums, are intended to produce passive immunity; they are "antibodies," which directly antagonize the invading bacteria and toxins.

The other great class of immunity products is called "antigens" because they are administered in the hope that their presence in the body will stimulate the production of antibodies.

This active immunity, formed by the introduction of antigens is, in general, slower in appearance but more lasting than the passive immunity caused by the introduction of foreign antibodies. It must be remembered also that the antigen is of the same nature as the organism causing the disease which is to be combated, and that in using antigens we are calling on the cells and fluids of the individual to produce their own protecting substances. To the class of antigens belong the vaccines, viruses, tuberculins, toxins, and bacterial vaccines.

These antigens and antibodies are of unknown chemical composition, of high molecular weight, and even when soluble, are not easily absorbed, without change, from the gastro-intestinal tract. Hence, they must be administered by the subcutaneous, intramuscular, intraspinal, or intravenous route in order to reach tissues not directly accessible.

The use of serums and serum preparations is sometimes followed by certain manifestations which are discussed under Normal Horse Serum. These are usually due to sensitization of the individual by horse serum and in certain cases may be avoided by the use of serums from the bovine species or from sheep or goats.

I. Non-Immune Serums

NORMAL HORSE SERUM.—Serum Equinum.—The serum of the blood of the normal horse obtained in a sterile manner and passed through a Berkefeld filter.

Actions and Uses.—Though not a specific immunity product, normal horse serum is classed commonly with the other serums. It is claimed that it is used with success in hemorrhagic conditions, to increase the coagulability of the blood.

The injection of horse serum is followed in certain individuals by more or less pronounced symptoms of anaphylactic shock. In its mildest form, this appears as an urticarial eruption on the skin or an edematous swelling of the mucous membranes. In more severe cases, there may be a fall of temperature, increased rapidity of pulse, quickened and difficult respiration, cyanosis, and occasionally convulsions. In rare cases, the attack comes on with great suddenness and may terminate fatally. These cases of sudden death occur especially in asthmatics and in patients who are naturally hypersensitive to horse serum. Ordinary serum disease manifests itself by milder but similar symptoms which appear from a few days to one or two weeks after the injection of the serum. In addition to the eruptions which are urticarial or scarlatiniform, joint pains and swelling of the joints sometimes occur.

Most cases of this poisoning have occurred after the use of antitoxic serums; but emphasis should be laid on the fact that these symptoms are not caused by antitoxin, but are due to hypersusceptibility to the proteins of horse serum.

Atropine and epinephrine, hypodermically, may be used for the severer manifestations of serum poisoning.

The Cutter Laboratory, Berkeley, Calif.

Normal Serum (from the Horse).—**Marketed in syringes containing 10 cc. and in bottles containing 25 cc.**

The Gilliland Laboratories, Inc., Marietta, Pa.

Normal Horse Serum.—**Marketed in syringes each containing 10 cc.; also in ampules containing 10, 25, 50 or 100 cc. as ordered.**

Lederle Antitoxin Laboratories, New York.

Normal Horse-Serum.—**Marketed in a special syringe containing 10 cc., with sterile needle. Also in an aseptic glass vial, containing 100 cc.**

Eli Lilly & Co., Indianapolis.

Normal Horse Serum.—**The serum of the blood of the normal horse obtained in a sterile manner and passed through a Berkefeld filter. Marketed in packages of one syringe containing 10 cc.; also in packages of one vial containing 20 cc.**

H. K. Mulford Company, Philadelphia.

Normal Serum (from the Horse).—Marketed in packages of one 10 cc. syringe (*M 90-09*); in packages of one 20 cc. syringe (*M 90-012*); in packages of one 50 cc. double ended vial (*M 90-010*).

Normal Horse Serum Without Preservative.—Marketed in packages of one vial containing 100 cc.

The National Drug Co., Philadelphia.

Normal Horse Serum.—Marketed in packages of one syringe containing 10 cc.; in packages of two syringes each containing 10 cc.; in packages of one vial containing 25 cc.; in packages of one double ended vial containing 50 cc.; also in packages of one double ended vial containing 100 cc.

Parke, Davis and Company, Detroit.

Normal Horse Serum-P. D. and Co.—**Marketed in packages containing one 10 cc. syringe container (*Bio. 50*); in packages containing one 10 cc. rubber-stoppered bulb (*Bio. 52*), and in packages containing one 30 cc. rubber-capped bulb (*Bio. 53*).**

E. R. Squibb & Sons, New York.

Normal Horse Serum.—**Marketed in packages of one and two syringes, each syringe containing 10 cc.; also in vials of 20 cc. each, without a syringe.**

United States Standard Products Company, Woodworth, Wis.

Normal Horse Serum.—Marketed in packages of one syringe containing 10 cc.; also in packages of one syringe containing 20 cc. The serum is preserved with 0.4 per cent of orthocresol.

II. Antibodies Used for Prophylactic or Therapeutic Purposes

Antibodies are usually directed against the toxins or soluble products of bacteria or against the bacteria themselves. All the antibodies enumerated below are formed in the blood serum of the larger domestic animals by active immunization; that is, by injecting the animal with an antigen. The animal is then bled to furnish the serum, which afterward may be purified, in the case of the antitoxins, to remove as many inactive substances as possible, leaving the antitoxin in a concentrated form.

PNEUMOCOCCUS ANTIBODY SOLUTION, TYPES I, II AND III COMBINED.—An aqueous solution of specific pneumococcus antibodies, types I, II and III, free from chemically demonstrable proteins of horse serum. The material is prepared by adding to the serum from horses immunized by repeated injections of pneumococci, types I, II and III, heavy emulsions of equal proportions of pneumococci, types I, II and III. After a suitable period for the combination of the antigen and antibody, the mixture is centrifuged and the sediment is washed with salt solution to rid it of horse serum. The washed sediment is emulsified in physiological solution of sodium chloride containing 0.25 per cent of sodium bicarbonate and then heated at 55 C. for from thirty minutes to one hour to cause dissociation of the antigen and the antibody. The mixture is centrifuged; the supernatant liquid removed, chilled, recentrifuged and filtered through a filter candle. The final product contains 0.035 mg. of nitrogen per cubic centimeter.

Actions and Uses.—There is some evidence that this antibody solution is of value in the treatment of lobar pneumonia.

H. K. Mulford Company, Philadelphia.

Pneumococcus Antibody Solution, Types I, II and III Combined-Mulford.—Marketed in packages (*M 48-010*) of one 50 cc. double-ended vials with one complete intravenous outfit.

ANTITOXINS

The antitoxins are among the most useful of the antibodies. As the name implies, they antagonize toxins. Though toxins may be secreted by plants other than the bacteria and by some animals, e. g., the snake, the typical toxins are the soluble poisons produced by diphtheria and tetanus bacilli.

Diphtheria and tetanus are dangerous diseases almost entirely on account of the action of these toxins, and conversely, their prevention or cure, when the organisms have once gained entrance to the body, depends on the work of the particular antitoxin. Though the presence of the toxin stimulates the body to produce antitoxin, this active immunity may not be enough to save life; and, at any rate, assistance by the injection of antitoxin, ready made in the blood serum of another animal, hastens the cure or may prevent the disease.

In some cases, eruptions occur after injection of antitoxin, rarely swelling and pain in the joints. In other cases, more severe symptoms have been observed and in a few instances sudden death has occurred. These conditions are due, not to the antitoxin but to the horse serum in which it is contained. (See Normal Horse Serum.)

ANAEROBIC ANTITOXIN.—An antitoxic serum prepared by immunizing animals against the anaerobic bacteria found in gangrenous wounds.

Actions and Uses.—Evidence has been published to indicate that the use of anaerobic toxin preparations may be of value in the treatment of gas gangrene.

The Cutter Laboratory, Berkeley, Calif.

Polyanaerobic Antitoxin.—An antitoxic serum prepared by immunizing horses with the toxins of *B. tetani, B. welchii, Vibrion septique* and *B. oedematiens.* When a sufficiently potent antitoxic serum is obtained, the horses are bled and the serum is separated and filtered. The unitage of the tetanus antitoxin and of the Welch bacillus antitoxin is determined according to the method prescribed by the U. S. Public Health Service. The antitoxic potency against *Vibrion septique* and *B. oedematiens* toxins is determined by estimation of the number of lethal doses (for the rabbit) which the serum will neutralize. The product is marketed in bottles containing 100 cc. of the serum, each 100 cc. containing at least 5,000 units of tetanus antitoxin, 75 units of Welch bacillus antitoxin, and sufficient antitoxin to neutralize 50,000 minimum lethal doses of *Vibrion septique* toxin and 100,000 minimum lethal doses of *B. oedematiens* toxin.

Dosage.—Initial therapeutic, 100 cc. or more, repeated every eight to twelve hours as required; prophylactic, usually 50 cc.

Lederle Antitoxin Laboratories.

Anaerobic Antitoxin (Polyvalent)-Lederle.—Gas Gangrene Antitoxin.—An antitoxic serum prepared by immunizing horses with gradually increasing doses of the toxin of B. tetani prepared according to the methods used in the manufacture of tetanus antitoxin, and of B. welchii and Vibrion septique both obtained from anaerobic broth cultures of the organisms. All three toxins are injected simultaneously into the horse. When a potent antitoxin serum (as indicated by potency tests applied to trial bleedings) is obtained, blood is drawn aseptically from the jugular vein and the clear serum is drawn off after the blood clots. The serum is clarified and sterilized. The potency tests used are made as follows: Tests for the content of tetanus antitoxin and B. welchii (perfringens) antitoxin are made according to the methods prescribed by the U. S. Hygienic Laboratory; for determining the strength of the Vibrion septique antitoxin, serial dilutions of the antitoxin are mixed with Vibrion septique toxin and the mixtures injected into rabbits, the Vibrion septique toxin having been previously standardized for its M.L.D. by injection into rabbits. The product is marketed in 100 cc. vials, each cubic centimeter containing 50 units of tetanus antitoxin, 2 units of perfringens (B. welchii) antitoxin, and sufficient Vibrion septique antitoxin to neutralize one thousand M.L.D. of the Vibrion septique toxin.

Dosage.—Initial doses of 100 to 200 cc., followed in six to eight hours by 100 cc., and every twelve hours thereafter by 100 cc. as required.

H. K. Mulford Company, Philadelphia.

Perfringens Antitoxin.—B. Welchii Antitoxin.—Anti-Gas Gangrene Serum.—An antitoxic serum prepared by immunizing horses with gradually increasing doses of the toxin of *B. welchii.* After the desired degree of potency is obtained, the horses are bled, the plasma is separated, and the serum is prepared in a manner similar to that used for other antitoxic serums. In the preparation of the concentrated product, a method is used which is similar to that used for concentrated diphtheria or tetanus antitoxin. The finished product is tested on pigeons by determining the minimum amount necessary to neutralize the M. L. D. of *B. welchii* toxin, the potency being expressed in units, each unit representing one thousand times this amount. The product is marketed in 100 cc. bottles of unconcentrated serum (M 36-68) containing at least one unit per cubic centimeter; in 50 cc. bottles of unconcentrated serum (M 36-37) containing at least two units per cubic centimeter; and in 20 cc. syringes of concentrated serum (M 51-012) containing at least five units per cubic centimeter.

Dosage.—For prophylaxis, 25 units; for treatment, initially from 40 to 100 units intramuscularly and 40 units intravenously, followed by 40 to 80 units intramuscularly at daily intervals as indicated.

Parke, Davis & Co., Detroit.

Tetanus-Perfringens Antitoxin Refined and Concentrated-P. D. & Co.—An antitoxic serum prepared from the toxins of *B. welchii* and *B. tetani.* Horses are immunized with repeated, gradually increasing doses of tetanus toxin and perfringens (*B. welchii*) toxins until the serum samples from treated animals show a potency of 400 units of tetanus antitoxin per cubic centimeter and one unit or more of perfringens antitoxin per cubic centimeter. Regular bleedings are then obtained from the treated animals and the serums stored at 2 C., after which they are chemically refined and concentrated. Both the tetanus and the perfringens antitoxins are tested and standardized according to the U. S. Hygienic Laboratory method. In addition to use in the treatment of gas gangrene, tetanus-perfringens antitoxin refined and concentrated-P. D. & Co. is proposed for use as a prophylactic in conditions such as wound or contusion in the abdominal tract and as curative in cases of acute peritonitis and obstruction of the small bowel. It is marketed in packages of 1 syringe (Bio 2025) containing 1500 units of tetanus antitoxin and 10 units of perfringens antitoxin.

Dosage.—Small initial doses (0.1 to 0.5 cc.) to avoid anaphylaxis; prophylactic, the contents of one syringe, repeated in six to eight hours and again in twelve to twenty-four hours if necessary; therapeutic, the contents of from one to two syringes, repeated daily if necessary.

BOTHROPS ANTITOXIN.—An antitoxic serum prepared by immunizing animals against the venom of the tropical American serpents of the genus *Bothrops.*

Actions and Uses.—In animal tests the venom of certain snakes may be neutralized by the employment of a serum obtained from animals that have been injected with venom from a snake of the same family. Bothrops antitoxin is used to neutralize the venom injected by the bite inflicted by members of the genus *Bothrops.*

Dosage.—The serum is administered intramuscularly or subcutaneously; in cases seen late or in the presence of severe symptoms it may be administered intravenously.

H. K. Mulford Company, Philadelphia.

Antivenin (Bothropic).—Tropical American Anti-Snake-Bite Serum.—An antitoxic serum prepared by injecting horses with venom from serpents of the genus *Bothrops,* especially of the "Fer-de-Lance" (*Bothrops atrox*). It is claimed to have neutralizing effect against the venom of the genus represented. The venom is extracted and promptly desiccated. It is dissolved in saline glycerin solution and injected subcutaneously into horses in fractional, gradually increasing doses until immunity has been established. The horses are bled and, after separation, the plasma is concentrated by a salting out process. Potency is determined by tests on pigeons, the maximum amount of venom neutralized by 1 cc. of the serum being taken as the titer of the product; this quantity must neutralize at least 2 mg. of the venom when tested on pigeons, mice and rabbits.

Marketed in syringes of 10 cc. (a single dose).

BOVINE TETANUS ANTITOXIN.—An antitoxin complying with the standards for tetanus antitoxin, U. S. P., except that it is made from the serum of cattle instead of from horse serum.

H. K. Mulford Co., Philadelphia.

Tetanus Antitoxin (Bovine).—An antitoxin derived from the blood serum of cattle immunized against the toxin of *B. tetani.* Marketed in packages of one syringe (M-97) containing 1,500 units (one immunizing dose).

CROTALUS ANTITOXIN.—An antitoxic serum prepared by immunizing animals against the venom of snakes of the crotalus family.

Actions and Uses.—Tests on animals show that the venom of certain snakes may be neutralized by the employment of a serum obtained from animals that have been injected with venom from a snake of the same family. Crotalus antitoxin is used to neutralize the venom injected by the bite inflicted by members of the crotalus family.

Dosage.—The serum is administered intramuscularly or subcutaneously; in cases seen late or in the presence of severe symptoms it may be administered intravenously.

H. K. Mulford Company, Philadelphia.

Antivenin (Nearctic Crotalidae). — North American Anti-Snake-Bite Serum.—An antitoxic serum prepared by injecting horses with venoms from serpents of the North American species of the family *Crotalidae* (Rattle Snake, 75 per cent; Copperhead, 12½ per cent; and Water Moccasin, 12½ per cent). It is claimed to have neutralizing effect against the venom of the species represented. The venom is extracted from the snakes and promptly desiccated. The mixture of the venoms is injected subcutaneously into horses in fractional doses until immunity is established. The animal is bled, and the plasma is concentrated by a salting out process. The potency of the product is determined by tests on pigeons, the maximum amount of venom neutralized by 1 cc. of the serum being taken as the titer of the product.

Marketed in syringes containing 10 cc. (a single dose).

ERYSIPELAS STREPTOCOCCUS ANTITOXIN.—An antitoxic serum prepared by immunizing animals against the toxin of the hemolytic streptococci of erysipelas.

Actions and Uses.—Reports have been published which suggest that the injection of erysipelas streptococcus antitoxin favorably affects the course of erysipelas by lowering the temperature, decreasing leukocytosis, causing the lesions to fade, and relieving the symptoms of toxemia.

Dosage.—There is no established dosage. Quantities recommended by various manufacturers vary from 12 cc. to

100 cc., to be repeated according to the influence or want of influence on the course of the infection. The unconcentrated serum is recommended for intravenous administration in maximum dosage; the concentrated, in smaller doses, either intravenously or intramuscularly.

Lederle Antitoxin Laboratories, New York.

Erysipelas Streptococcus Antitoxin (Lederle) Refined and Concentrated.—An antitoxic serum prepared by immunizing horses by subcutaneous injections of the toxic filtrate obtained from broth cultures of the erysipelas streptococcus, or by intravenous injection of cultures of the erysipelas streptococcus obtained from typical cases of erysipelas. When test bleedings show the serum to have reached a sufficient degree of potency, the horses are bled aseptically into sodium citrate and the plasma is refined and concentrated by a method similar to the Park-Banzhaf process. Potency is tested by making serial dilutions of the serum with equal volumes of a dilution of erysipelas toxin of such strength that 0.1 cc. of the toxin-antitoxin mixture will contain 1 skin test dose of toxin; these are injected intradermally into goats, the highest dilution of antitoxin in the mixture indicating the potency of the product. Erysipelas streptococcus antitoxin (Lederle) refined and concentrated is administered in early cases of moderate severity in one "basic dose" (the entire content of one syringe as marketed) intramuscularly, repeated if necessary at intervals of twenty-four hours until the erysipelatous blush disappears; in late and severely toxic cases, dosage up to five or six basic doses intramuscularly or, in extreme cases, intravenously, is recommended. It is marketed in packages of one syringe containing one basic dose.

Eli Lilly & Company, Indianapolis.

Erysipelas Streptococcus Antitoxin-Lilly (Concentrated Globulin).—The antitoxin is obtained by injecting horses subcutaneously with strains of hemolytic streptococci obtained from human cases of erysipelas. It is concentrated by a method similar to that employed in the refinement of diphtheria antitoxin. The antitoxin is standardized by determining how many skin test doses of toxin each cubic centimeter of the antitoxin will neutralize. The product is marketed in syringe containers (therapeutic dose) containing 5,000 "units."

H. K. Mulford Co., Philadelphia.

Erysipelas Streptococcus Antitoxin (Concentrated)-Mulford.—This antitoxic serum is prepared by injecting horses intradermally with strains of hemolytic streptococci isolated by H. Amoss from human cases of erysipelas lesions, bleeding the horses and when test bleedings show the serum to have reached the desired potency, separating the serum, sterilizing it, and preserving by the addition of 0.35 per cent of phenol. The product is then concentrated by a process which preserves both the antitoxic and antibacterial properties claimed to be in the original serum. Erysipelas streptococcus antitoxin (concentrated)-Mulford is standardized in terms of "protective units" (1 unit being one-tenth of the amount of erysipelas streptococcus antitoxin required to protect 66 per cent of the mice injected with one minimal fatal dose of a virulent culture of erysipelas streptococci). It is administered in doses of 20 cc., given intramuscularly, and repeated within twelve to twenty-four hours if indicated. Marketed in packages of one 20 cc. syringe containing 1,000,000 protective units and accompanied by sterile, glass-encased needle. Also marketed in packages of one 10 cc. syringe containing 500,000 protective units, the unit being defined as one-tenth of the amount of erysipelas streptococcus antitoxin required to protect 66 per cent of the mice injected with one minimal fatal dose of a virulent culture of erysipelas streptococci.

Parke, Davis & Co., Detroit.

Erysipelas Streptococcus Antitoxin Refined and Concentrated-P. D. & Co.—This antitoxin is prepared by immunizing horses with cultures of streptococcus isolated from erysipelas. The blood serum is withdrawn from the immunized animals and is concentrated and refined by methods similar to those used for other antitoxins. The antitoxin is standardized by determining how many skin test doses of toxin each cubic centimeter of the antitoxin will neutralize. The potency of the marketed product is declared in "units," a unit representing the amount of antitoxin required to neutralize one skin test dose of toxin. The product is claimed to possess both antitoxic and antibacterial properties. It is marketed in packages of one piston syringe containing 500,000 units.

E. R. Squibb & Sons, New York.

Erysipelas Streptococcus Antitoxin Concentrated-Squibb.—This antitoxin is prepared according to the method of K. E. Birkhaug under license of the School of Medicine and Dentistry of the University of Rochester. It is obtained by immunizing horses by repeated injections of the toxic filtrate from a number of strains of hemolytic streptococci of erysipleas furnished by Birkhaug and the injection of living cultures of the streptococci. The antitoxin thus obtained is concentrated by a modification of the Banzhaf method, preserved by the addition of 0.4 per cent of cresol, and standardized by determining its neutralizing power against a specific toxin furnished by the licensor. The product is marketed in packages of one syringe containing 10 cc., each cubic centimeter of which will neutralize more than 50,000 skin test doses of toxin.

SCARLET FEVER STREPTOCOCCUS ANTITOXIN.—An antitoxic serum prepared by immunizing animals against the toxin of the hemolytic streptococcus of scarlet fever. It is prepared (*a*) after the method of G. F. Dick and G. H. Dick by immunizing horses by injecting the soluble toxin of strains of hemolytic streptococci that have produced experimental scarlet fever in human beings and (*b*) by the method of A. R. Dochez in which horses are immunized against the specific scarlet fever organism by the localization of the living streptococci in a subcutaneous agar nodule which grows and stimulates the production of antitoxic and antibacterial substances. Certain modifications of these methods are employed by some producers.

Scarlet fever streptococcus antitoxin is standardized in terms of units, each unit being capable of neutralizing ten test doses of toxin, each test dose containing about five skin test doses. Each package is required to bear an expiration date, after which it should not be used.

Actions and Uses.—During recent years much evidence has accumulated to show that the specific organism of scarlet fever (*Streptococcus hemolyticus-scarlatinae*) has been determined and that the administration of a serum containing the antitoxin produced by this organism influences the course of scarlet fever. It is also believed that temporary immunity against scarlet fever may be established through the use of such a serum. The serum is also used to distinguish the rash of scarlet fever from other rashes by the production of a blanched area at the site of its intradermal injection.

Cutter Laboratory, Berkeley, Calif.

Scarlet Fever Streptococcus Antitoxin-Cutter.—It is prepared by the method of Drs. Dick under U. S. patent 1,547,396 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. The serum is concentrated by a modification of the Banzhaf method. Marketed in packages of one syringe containing 2,000 units (prophylactic dose), and in packages of one syringe containing 6,000 units (therapeutic dose).

Lederle Antitoxin Laboratories, New York.

Scarlet Fever Streptococcus Antitoxin-Lederle (Refined and Concentrated).—It is prepared by immunizing horses according to the method outlined by Dr. A. R. Dochez as follows: Horses are injected subcutaneously with about 30 cc. of melted nutrient agar. The needle is left in place, the syringe detached, and another syringe containing a broth culture of the Dochez strain (N. Y. 5) of scarlatinal streptococcus is attached to the same needle. This culture is expelled into the agar plaque. This immunizing process is repeated until test bleedings show the serum to be of the desired potency. The horses are then bled aseptically into sodium citrate and the plasma is refined and concentrated by a method similar to the Park-Banzhof process. Marketed in packages of one syringe containing 1,500 units (prophylactic dose); and in packages of one syringe containing 5,000 units (therapeutic dose).

Eli Lilly & Company, Indianapolis.

Scarlet Fever Streptococcus Antitoxin-Lilly (Refined and Concentrated).—It is prepared by the Dochez method. The serum is concentrated by the method employed in concentrating diphtheria antitoxin. Marketed in packages of one syringe (therapeutic dose) containing 6,000 units, and in packages of one syringe (prophylactic dose) containing 1,500 units.

H. K. Mulford Company, Philadelphia.

Scarlet Fever Streptococcus Antitoxin Concentrated.—It is prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. The serum is concentrated by the method employed in concentrating diphtheria antitoxin. Marketed in packages of one syringe (M. 53-207) containing 2,000 units (prophylactic dose) and in packages of one syringe (M. 53-012) containing 6,000 units (therapeutic dose); also marketed in single 1 cc. vial packages (for the diagnostic blanching test) containing sufficient scarlet fever antitoxin for five tests.

Parke, Davis & Co., Detroit.

Scarlet Fever Streptococcus Antitoxin-P. D. & Co.—It is prepared by inoculating horses with scarlet fever streptococcus toxin and live virulent cultures of scarlet fever streptococci, under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in packages of one syringe (prophylactic dose) containing 2,000 units (Bio. 116); in packages of one syringe (therapeutic dose) containing 6,000 units (Bio. 115); and in single 1 cc. vials (for the diagnostic blanching test) containing sufficient scarlet fever antitoxin for five blanching tests (Bio. 151).

E. R. Squibb & Sons, New York.

Scarlet Fever Streptococcus Antitoxin Concentrated.—It is prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires, 1942) by license of the Scarlet Fever Committee, Inc. The serum is concentrated by the Banzhaf method. Marketed in packages of one syringe containing 2,000 to 2,500 units (prophylactic dose); in packages of one syringe containing 5,000 to 6,000 units (therapeutic dose); and in packages of 1 cc. vials (for the diagnostic blanching test) containing sufficient scarlet fever antitoxin for ten blanching tests.

United States Standard Products Co., Woodworth, Wis.

Scarlet Fever Streptococcus Antitoxin-U. S. S. P.—It is prepared by the injection of killed or attenuated broth cultures of hemolytic streptococcus isolated from typical cases of scarlet fever. The serum is concentrated by a modification of the Banzhaf method. The product contains not more than 20 per cent of solids and is preserved with 0.4 per cent of cresol. Marketed in packages of one syringe containing 1,500 units (prophylactic dose), and in packages of one vial containing 5,000 units (therapeutic dose).

ANTIBACTERIAL SERUMS

More complex in action than the antitoxins and much less satisfactory for therapeutic purposes are those antibodies which resist the bacteria themselves. This field of usefulness is open to much controversy, both theoretical and practical.

ANTI-ANTHRAX SERUM.—Serum Antianthracicum.—A serum prepared by immunizing horses against virulent anthrax bacilli.

Actions and Uses.—Good results have generally been reported from the use of the specific serum in human anthrax. Protective antibodies can be demonstrated experimentally.

Dosage.—From 30 to 100 cc., subcutaneously or intravenously. The serum should be used as early as possible and used freely, the dose being repeated several times a day in severe cases.

Lederle Antitoxin Laboratories, New York.

Anti-Anthrax Serum.—Initial doses of from 50 to 100 cc. may be administered intramuscularly or intravenously, to be repeated in twenty-four hours if indicated. Marketed in packages containing one 50 cc. syringe with bulb and sterile needle; also in packages of one 20 cc. vial.

H. K. Mulford Company, Philadelphia.

Anti-Anthrax Serum-Mulford.—Marketed in packages of two syringes (*M 2-08*) of 10 cc. each; in packages of one syringe (*M 2-012*) of 20 cc.; in packages of one double ended vial (*M 2-010*) of 50 cc. At least from 80 to 100 cc. should be injected intravenously as the initial dose.

Parke, Davis & Company, Detroit.

Anti-Anthrax Serum: Marketed in syringes containing 50 cc. (*Bio. 45*). Initial dose of from 50 to 100 cc., injected intravenously, should be followed by further injection in six or more hours. It is well to test the sensitization of the patient to horse serum, prior to the first injection, by means of the cutaneous test, which will require about one-half hour. The drop of serum required for this test can be obtained directly from the syringe container of anti-anthrax serum.

ANTIDYSENTERIC SERUM.—Serum Antidysentericum.—The serum (polyvalent) of horses immunized against the Shiga bacillus, its products of growth, and other types of the dysentery bacillus.

Actions and Uses.—A reduction in the mortality rate of bacillary dysentery through the use of some serums has been reported by some observers but not confirmed by all. It would seem that the best results may be ascribed to an antitoxic action in infections with the Shiga-Kruse type of bacillus. Infections with the Flexner, Harris or Hiss-Y strains, which are relatively poor in toxin production, have not been so favorably affected, though some bactericidal action is claimed. The most favorable results are observed in the early stage of the disease.

The serum is required to show a high agglutinin titer for the various types of dysentery bacilli.

Dosage.—From 20 to 100 cc., subcutaneously.

Lederle Antitoxin Laboratories, New York.

Antidysenteric Serum (*Polyvalent*).—From horses hyperimmunized against the Shiga, Kruse, Flexner and Hiss types of dysentery bacilli. Marketed in syringes containing 10 cc. each with sterile needle; also in syringes containing 50 cc. each with sterile needle.

Dosage.—For prophylaxis: 10 cc. injected subcutaneously. For treatment: an initial dose of from 50 to 100 cc. (preferably injected intravenously) and repeated at four-hour intervals as indicated by symptoms.

H. K. Mulford Company, Philadelphia.

Antidysenteric Serum (*Polyvalent*).—From horses immunized against the Shiga, Flexner and Y strains of the dysentery bacillus. Marketed in packages of one syringe (*M 25-012*), containing 20 cc. each; also in packages of one vial (*M 25*), containing 50 cc. each, with or without sterile needle and sterile rubber tubing for intravenous injection.

Dosage.—Fifty to 100 cc., to be followed at eight hour intervals by doses of 50 cc. until 400 cc. have been given. Prominent authorities recommend intravenous injection.

Parke, Davis & Co., Detroit.

Antidysenteric Serum.—From horses immunized against several strains of Shiga, Flexner and Hiss-Y types of dysentery bacilli. Marketed in packages of one vial (*Bio. 122*), containing 20 cc.; also in packages of one syringe (*Bio. 123*), containing 20 cc.

Dosage.—10 cc. is suggested as prophylactic dose; therapeutic dose, 60 to 100 cc., preferably intravenously.

ANTIMENINGOCOCCUS SERUM.—Serum Antimeningococcicum.—A polyvalent serum prepared by the immunization of horses with cultures of the various types of meningococci associated with meningitis in America (*Diplococcus intracellularis*).

Actions and Uses.—Greater success seems to have attended the use of serum directed against the meningococcus than has been the case with any other antibacterial serum. The serum must be introduced into the subdural space and its action is due probably in part to bacteriotropins, possibly to anti-endotoxins and other antibodies as well. Each lot of the serum is required to be tested for potency by means of agglutination or complement fixation methods and none is allowed to be sold which does not reach a reasonable titer against the several types of meningococci by at least one of the tests.

Each lot is tested at the Hygienic Laboratory prior to sale.

Dosage.—Average dose, 30 cc. intraspinally, as early as possible in the disease and repeated as indicated. For young children the dose should be 20 cc. The serum should be introduced slowly by gravity after the removal of a corresponding amount of cerebrospinal fluid. The administration of the serum should be controlled by blood pressure readings, a drop of 10 mm. of mercury during administration being the signal for withdrawal of the needle.

The Gilliland Laboratories, Inc., Marietta, Pa.

Antimeningococcic Serum.—Marketed in packages of one vial containing 15 cc., with sterile needle, stylet, and attachments for intraspinal administration; in packages of two vials each containing 15 cc. with sterile needle, stylet, and attachments for intraspinal administration.

Dosage.—The recommended intraspinal dosage for the treatment of epidemic cerebrospinal meningitis is from 5 to 15 cc. for a child, and 30 cc. or more for an adult.

Lederle Antitoxin Laboratories, New York.

Antimeningococcic Serum.—Marketed in cylinders containing, respectively, 15 and 30 cc., each with sterile needle and stylet; also in 20 cc. vials.

Dosage.—Usually from 5 to 15 cc. for infants and children and 30 cc. or more for adults are given at each dose, which should be repeated at twenty-four hour intervals. The treatment of one case usually requires 120 cc. or more.

Eli Lilly & Co., Indianapolis.

Antimeningococcic Serum Concentrated, Lilly.—Refined and concentrated by the Banzhaf method. Marketed in packages of one 10 cc. double ended vial with apparatus for intraspinal injection.

H. K. Mulford Company, Philadelphia.

Antimeningitis Serum.—Marketed in double ended vials (*M 30-011*), each containing 15 cc., with sterilized rubber tubing and sterilized intraspinal needle and stylet for injections by the gravity method.

Dosage.—From 15 to 30 cc. at intervals of twenty-four hours.

Parke, Davis & Company, Detroit.

Antimeningococcic Serum: Marketed in packages of two syringes, with flexible connection, gravity tube and needle with stylet (*Bio. 170*), each containing 15 cc.; also in packages of one syringe, with needle and long flexible tube, suitable for intravenous injection either by pressure or gravity method (*Bio. 172*) each containing 50 cc.

Dosage.—From 50 to 150 cc., intravenously; from 15 to 30 cc., intraspinally.

E. R. Squibb & Sons, New York.

Antimeningococcic Serum.—Marketed in packages of two 15 cc. containers in a gravity outfit with needle and trocar.

ANTIPNEUMOCOCCUS SERUM.—Serum Antipneumococcicum.—A serum obtained from horses immunized by injection of virulent pneumococci.

Actions and Uses.—Investigations indicate that the pneumococcus in lobar pneumonia may be referred to one of four serological types. Type I serum alone is worthy of clinical trial. Early massive (from 50 to 100 cc.) intravenous doses of a highly potent serum are used.

The Gilliland Laboratories, Inc., Marietta, Pa.

Antipneumococcic Serum Type I.—Marketed in vials containing 50 cc. and 100 cc.; also in double ended vials containing 50 cc. each, with a gravity injecting apparatus for intravenous injection.

Lederle Antitoxin Laboratories, New York.

Antipneumococcus Serum, Type 1.—Marketed in packages of one cylinder containing 50 cc., with complete intravenous outfit; in packages of one cylinder containing 100 cc., with complete intravenous outfit; in packages of one vial containing 100 cc.

H. K. Mulford Company, Philadelphia.

Antipneumococcic Serum, Type I.—Prepared by immunizing horses with dead and living pneumococci Type I and standardized by animal potency tests against a highly virulent Type I culture. Marketed in packages of one 50 cc. double ended vial (*M 41-010*).

Parke, Davis & Company, Detroit.

Antipneumococcic Serum, Type I.—Marketed in a piston syringe containing 50 cc.

E. R. Squibb & Sons, New York.

Antipneumococcic Serum, Type I.—Marketed in vials containing 50 cc.; also marketed in packages of one 50 cc. gravity container.

III. Agents for Producing Active Immunity

The use of substances for the production of active immunity has at least two advantages over the use of serums: The antibodies formed in the patient's own serum are not lost so rapidly as antibodies from the serum of another species, and, in the second place, not only are the immunity reactions of the blood serum made use of, but the fixed cells of the body may also take part in the immunizing process. Thus, protection from smallpox conferred by vaccination lasts for years, while the prophylactic action of diphtheria antitoxin is of avail only for days.

These advantages are frequently offset, however, by the tardiness and uncertainty with which active immunity appears and by the fact that the body may already be overloaded with antigen in the disease or that sufficient antigen to produce an effect would be in itself harmful to the patient.

Antigens may be of various sorts. Thus vaccine virus, the most notably successful, is conceded to be the living microorganisms attenuated by passage through the bovine species. Other antigens, such as tuberculins and bacterial vaccines, consist of killed whole bacteria or of products formed by them or extracted from them.

ATTENUATED LIVING VIRUSES

ANTIRABIC VACCINE.—Vaccinum Rabies.—Antirabic vaccine or antirabic virus is the virus of rabies rendered practically nonvirulent for man by passage through a long series of rabbits and treated in various ways to decrease the infectivity still further to destroy it. Methods of treating the virus before inoculation are drying (Pasteur), dilution (Högyes), emulsification with phenol (Semple, Fermi), drying at very low temperature (Harris), and dialyzing (Cummings).

Actions and Uses.—By treatment with antirabic vaccine after the bite of a rabid animal, immunity is usually established before the incubation period of the disease is completed, and rabies is thus prevented. The treatment fails occasionally, and in a small percentage of cases it is followed by paralysis, which is usually transient but may be fatal.

Cutter Laboratory, Berkeley, Calif.

Rabies Vaccine (Semple).—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brains of rabbits killed on the sixth day after inoculation with fixed virus rabies are ground in a mortar with physiological solution of sodium chloride containing 1 per cent. of phenol to yield a 2 per cent. suspension of brain substance. The mixture is strained, incubated at 37 C. for twenty-four hours and then diluted with an equal volume of physiological solution of sodium chloride so that the finished product contains 1 per cent. of brain substance. Marketed in packages of seven syringes, each containing 2.5 cc. The content of a syringe is administered daily over a period of from fourteen to twenty-eight days according to the severity of the case.

The Gilliland Laboratories, Inc., Marietta, Pa.

Pasteur Anti-Rabic Vaccine.—The virus is prepared in accordance with the general method of the U. S. Public Health Service. One-fifth of an inch of dried cord, emulsified in 0.6 cc. of 60 per cent glycerin containing 0.3 per cent trikresol is supplied. This is diluted with 2.5 cc. of sterile physiological solution of sodium chloride in syringes; the dilution is made at the time of injection. The treatment consists of twenty-one doses which are administered at twenty-four hour intervals, and these are sent in three instalments of seven doses each. The instalments are sent by special delivery mail. The first dose consists of two sections of a cord dried for six days; the second dose consists of two sections of a cord dried for five days; and the third dose two sections of a cord dried for four days. The remaining eighteen doses are prepared from single sections of cords dried as follows: 3, 3, 2, 2, 1, 5, 4, 4, 3, 3, 2, 2, 4, 3, 2, 3, 2, 1, and they are administered in the order listed.

Rabies Vaccine-Gilliland (Semple Method).—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brain and cord of rabbits killed after inoculation with fixed rabies virus are emulsified in a ball mill, after which a sufficient quantity of physiologic solution of sodium chloride containing 1 per cent of phenol is added to yield an 8 per cent emulsion of the fixed virus. The emulsion is incubated at 37.5 C. for twenty-four hours and then diluted with an equal volume of physiologic solution of sodium chloride so that the finished product contains 4 per cent of the brain and cord substance in 0.5 per cent phenol. Marketed in packages of fourteen syringes each containing 2 cc. The content of a syringe is administered daily over a period of fourteen days.

Dr. D. L. Harris' Laboratory, St. Louis (National Pathological Laboratories, Chicago).

Rabies Vaccine (Harris).—Brains and spinal cords of rabbits that have died of fixed virus rabies infection, are ground to a paste, which is frozen in a container surrounded with carbon dioxide snow. The mass is pulverized and rapidly dried *in vacuo.* The resulting dry powder is standardized by the method devised by Dr. Harris, and stored *in vacuo* in the cold. One dose is given daily over a period of ten days or more, the early doses increasing in unitage up to a maximum. Each package contains vaccine and apparatus for the administration of one complete treatment, consisting of 10 tubes of rabies vaccine (Harris), sealed in a vacuum, and numbered consecutively; 10 vials containing physiological solution of sodium chloride for preparing the vaccine solution; and a Luer syringe with needle.

Jensen-Salsbery Laboratories, Inc., Kansas City, Mo.

Rabies Vaccine (Human), Phenol Killed.—The virus is prepared according to the general method of David Semple. The brain and cord, removed from a rabbit paralyzed on the sixth, seventh, or eighth day following a subdural inoculation of fixed virus rabies, are tested for sterility before emulsifying, then reduced to a fine suspension by shaking in a sterile bottle containing beads. The virus is killed by suspending the brain and cord substance in a sterile 1 per cent phenol saline solution in proportion of 4 per cent brain substance. This resulting suspension is kept at 37 C. for 24 hours; finally it is diluted with an equal volume of sterile physiological solution of sodium chloride, so that the product as sold contains brain substance, 2 per cent and phenol, 0.5 per cent. Marketed in packages containing 14 vials and a syringe, and in packages containing 21 vials and a syringe. The content of vial 1 and of vial 2 is administered on the first day of treatment allowing 4 to 6 hour intervals; the other doses are administered in sequence at 24 hour intervals until the treatment is completed.

Lederle Antitoxin Laboratories, New York.

Rabies Vaccine-Lederle (Semple Method).—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brains of rabbits killed on the seventh or eighth day after inoculation with fixed virus rabies are ground in a ball mill for four days with physiological solution of sodium chloride containing 1 per cent phenol to yield an 8 per cent suspension of brain substance. The mixture is incubated at 37 C. for twenty-four hours and then diluted with an equal volume of physiological solution of sodium chloride so that the finished preparation contains 4 per cent of brain substance. Marketed in packages of fourteen syringes each containing 2 cc. The content of a syringe is administered daily over a period of fourteen days.

Eli Lilly & Company, Indianapolis.

Pasteur Antirabic Preventive Treatment (Harris Modification).—Brains and spinal cords of rabbits, that have died of fixed virus rabies infection, are ground to a paste which is frozen by the addition of carbon dioxide snow. The mass is pulverized and rapidly dried *in vacuo*. The resulting dry powder is standardized by the method devised by Dr. Harris, and stored *in vacuo* in the cold. A dose of 1 cc. is given daily over a period of fourteen days, the earlier doses increasing in unitage up to a maximum. Supplied in emulsion in 1 cc. syringes, ready for use. A package containing the first seven doses is sent out from the nearest Lilly depot; a second package containing the last seven doses freshly prepared is sent out from the home office in time to insure continuous treatment.

H. K. Mulford Company, Philadelphia.

Rabies Vaccine.—The vaccine is prepared according to the method of Pasteur. A complete treatment (*M475-99*), consisting of twenty-one doses, is furnished. Complete description and directions accompany each outfit.

Rabies Vaccine (Phenol Killed)-Mulford.—The virus is prepared according to the general method of David Semple. It consists of a sterile suspension of the brain tissue of rabbits moribund from the injection of virulent fixed strain of rabies. The virus is killed by the use of phenol and by incubation at 37.5 C. for twenty-four hours. Marketed in packages of 14 doses, each dose consisting of 2 cc., contained in a syringe. All the doses are of the same potency; one dose is to be given daily over a period of fourteen days.

The National Drug Co., Philadelphia.

Rabies Vaccine-Human (Semple Method).—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brains and spinal cords of rabbits killed on the sixth or seventh day after inoculation with fixed virus rabies are ground with physiological solution of sodium chloride containing 1 per cent of phenol to yield an 8 per cent suspension of brain substance.

The mixture is incubated at 37 C. for twenty-four hours and then diluted with an equal volume of physiological solution of sodium chloride so that the finished product represents a 4 per cent emulsion marketed in sets of two packages, the first containing four 2 cc. vials and the second containing ten 2 cc. vials. All the doses are of the same potency; one dose is to be given daily over a period of fourteen days.

Parke, Davis and Company, Detroit.

Rabies Vaccine (Cumming).—The virus is prepared by dialyzing a 1 per cent suspension of brain tissues (from a rabbit dying of rabies induced by an injection of fixed virus) against running water until the active virulent virus is destroyed. The treatment is divided into two classes: mild, requiring 14 doses; severe, requiring 21 doses. One dose, 2 cc., is given daily over a period of either 14 or 21 days. Each package (*Bio. 440*) consists of seven syringe containers of 2 cc. each (1 dose).

E. R. Squibb & Sons, New York.

Pasteur Antirabic Vaccine.—The virus is prepared according to the method of the Hygienic Laboratory, Washington, D. C. An amount of the dried cord sufficient for one dose is suspended in a mixture of 66⅔ per cent glycerin and 33⅓ per cent physiological solution of sodium chloride. The treatment consists of twenty-one daily treatments, each in an aseptic, sealed ampule, with syringe.

Rabies Vaccine (Semple Method)-Squibb.—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brains of rabbits killed on the sixth day after inoculation with fixed virus rabies, are ground in a ball mill with physiological solution of sodium chloride containing 1 per cent of phenol to yield a 10 per cent suspension of brain substance. The mixture is incubated at 37 C. for twenty-four hours and then diluted with an equal volume of physiological solution of sodium chloride so that the finished product contains 5 per cent of brain substance. Marketed in packages of fourteen syringes, each containing 2 cc. The content of a syringe as administered daily over a period of fourteen days.

Pasteur Institute of St. Louis, St. Louis.

Antirabic Virus (Semple).—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). It consists of a sterile suspension of the brain tissue of rabbits moribund from the injection of a virulent fixed strain of rabies. The virus is killed by the use of phenol and by incubation at 37.5 C. for twenty-four hours. Marketed in packages of fourteen doses, each dose consisting of 2 cc., contained in an ampule. All the doses are of the same potency; one dose is to be given daily over a period of fourteen days.

Terrell's Laboratories, Fort Worth, Texas.

Rabies Vaccine (Phenolized).—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brain and cord of rabbits killed after inoculation with fixed virus rabies are ground in a mortar with distilled water containing 2 per cent of phenol to yield a 6 per cent emulsion of the fixed virus. The emulsion is incubated at 37 C. for forty-eight hours and then diluted with distilled water so that the finished product contains 1.5 per cent of the brain and cord substance and 0.5 per cent phenol. Marketed in packages of fourteen vials each containing 3 cc., and in packages of twenty-one vials each containing 3 cc. The content of a vial is administered daily over a period of from fourteen to twenty-one days according to the severity of the case. Ordinarily one dose is given daily but under certain conditions, such as badly lacerated wounds, bites in children, bites about the face and those who have been bitten some time before treatment is begun, two doses may be given daily for the first few days, then one dose daily until treatment is finished.

United States Standard Products Company, Woodworth, Wis.

Rabies Vaccine-U. S. S. P. (Semple Method).—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brains of rabbits killed after inoculation with fixed virus rabies are placed in a bottle containing beads and 1 per cent phenol solution. The bottle is thoroughly shaken, the resultant emulsion passed through a 100 mesh screen, and sufficient 1 per cent phenol solution added to yield an 8 per cent suspension of brain substance. The emulsion is incubated at 37 C. for twenty-four hours and then diluted with an equal volume of physiological solution of sodium chloride so that the finished product contains 4 per cent of brain substance in 0.5 per cent phenol. Marketed in packages of fourteen syringes, each containing 2 cc. The content of a syringe is administered daily over a period of fourteen days.

TOXIN-ANTITOXIN MIXTURE

DIPHTHERIA TOXIN-ANTITOXIN MIXTURE.—Mistura Toxini Diphtherici et Antitoxini Diphtherici.—It is well established that a far more durable immunity against diphtheria is produced by the use of a mixture of diphtheria toxin and diphtheria antitoxin than by the latter alone. The immunity does not appear until a considerable period of time has elapsed and for this reason the mixture is not applicable in the presence of an outbreak of the disease, in which case it is better to use an immunizing dose of antitoxin alone.

The toxin-antitoxin mixture finds its greatest field of usefulness in the immunization of the inmates of children's homes and asylums, of children below school age, of schoolchildren and of those who often come in contact with diphtheria. Three doses of 1 cc. each are usually given a week apart and this suffices to produce immunity in more than three-fourths of the instances. A Schick test performed about six months later determines whether further immunization is needed.

The requirements of the U. S. Public Health Service for diphtheria toxin-antitoxin mixture are that it shall be sterile and labeled to show the volume of each human dose and the number of L+ doses of toxin contained in each human dose. The toxin must be so neutralized with antitoxin that five human doses shall cause acute death in a guinea-pig, while one human dose should not cause death acutely.

The antitoxin used in the toxin-antitoxin mixture is produced from the horse, goat or sheep.

Cutter Laboratory, Berkeley, Calif.

Diphtheria Toxin-Antitoxin Mixture, 0.1 L+.—Each cubic centimeter of the mixture represents 0.1 L+ dose of diphtheria toxin neutralized with the required amount of antitoxin. Marketed in packages of three 1 cc. vials, representing one complete immunization; in packages of thirty 1 cc. vials, representing ten complete immunizations; in packages of one vial containing 30 cc.

The Gilliland Laboratories, Inc., Marietta, Pa.

Diptheria Toxin-Antitoxin Mixture, 0.1 L+.—Each cubic centimeter represents 0.1 L+ dose of diphtheria toxin neutralized with the required amount of diphtheria antitoxin. Marketed in packages of 3 ampules, each ampule containing 1 cc.; in packages of 30 ampules, each ampule containing 1 cc.; in packages of 3 syringes, each syringe containing 1 cc.; and in ampules containing, respectively, 10 cc., 20 cc. and 30 cc.

Lederle Antitoxin Laboratories, New York.

Diphtheria Toxin-Antitoxin Mixture (0.1 L+).—A mixture containing 0.1 lethal dose of diphtheria toxin neutralized with the required amount of diphtheria antitoxin. Marketed in packages of three vials, each containing 1 cc.; in packages of thirty vials, each containing 1 cc.; also in vials containing 30 cc.

Eli Lilly & Co., Indianapolis.

Diphtheria Toxin-Antitoxin Mixture 0.1 L+.—Each cubic centimeter contains 0.1 L.+ dose of diphtheria toxin neutralized with the required amount of sheep diphtheria antitoxin. Marketed in packages of three 1 cc. vials; in packages of one 30 cc. vial; in packages of ten vials, each containing three doses.

H. K. Mulford Co., Philadelphia.

Diphtheria Toxin-Antitoxin Mixture, New Formula (Park-Banzhaf's 0.1 L+).—Each cubic centimeter of the mixture constitutes a single dose containing 0.1 lethal dose (1/10 L+) of toxin properly neutralized with the necessary amount of diphtheria antitoxin marketed in packages of three 1 cc. vials (*M 72-253*) representing one immunizing treatment; in packages of thirty 1 cc. vials (*M 72-255*) representing ten immunizing treatments; also in packages of one 30 cc. vial (*M 72-73*) representing ten immunizing treatments of three doses each; also marketed in packages of one 10 cc. vial (*M 72-024*) representing three immunizing treatments.

The National Drug Co., Philadelphia.

Diphtheria Toxin-Antitoxin Mixture (Diphtheria Prophylactic).—Each cubic centimeter represents 0.1 L+ dose of diphtheria toxin neutralized with the required amount of antitoxin produced from goats, marketed in packages of three 1 cc. vials, one immunization; in packages of one 15 cc. vial, five immunizations; in packages of one 30 cc. vial, ten immunizations, and in packages of thirty 1 cc. vials, ten immunizations.

Parke, Davis & Company, Detroit.

Diphtheria Toxin-Antitoxin Mixture, 0.1 L+.—Diphtheria Prophylactic: Each cubic centimeter of the mixture represents 0.1 L+ dose of diphtheria toxin neutralized with the required amount of antitoxin produced from goats. Marketed in packages of 3 bulbs, each containing 1 cc. (*Bio. 67*) representing one immunizing treatment; also in rubber-capped vials containing 30 cc. (*Bio. 69*); also marketed in packages of 30 bulbs (*Bio. 68*) each containing 1 cc., representing ten immunizing treatments.

E. R. Squibb & Sons, New York.

Diphtheria Toxin-Antitoxin Mixture (New Formula)-Squibb.—Each cubic centimeter represents 0.1 L+ dose of diphtheria toxin neutralized with the required amount of diphtheria antitoxin produced from the horse. Marketed in packages of three ampules, each ampule containing 1 cc. of the mixture; and in ampules containing, respectively, 10 cc. and 20 cc. of the mixture; also marketed in packages of thirty 1 cc. ampules.

Diphtheria Toxin-Antitoxin Mixture (New Formula) (Sheep)-Squibb.—Each cubic centimeter represents 0.1 L+ dose of diphtheria toxin neutralized with the required amount of antitoxin obtained from the sheep. Marketed in packages of three ampules, each ampule containing 1 cc. of the mixture; in vials containing, respectively, 10, 20 and 30 cc.; and in packages of thirty 1 cc. ampules.

United States Standard Products Company, Woodworth, Wis.

Diphtheria Toxin-Antitoxin Mixture, 0.1 L+.—Each cubic centimeter of the mixture constitutes a single dose of diphtheria toxin, neutralized with the proper amount of antitoxin and preserved with 0.5 per cent phenol. Marketed in packages of 3 vials, each containing 1 cc; in packages of 30 vials, each containing 1 cc.; also in packages of 1 vial containing 30 cc.

Diphtheria Toxin-Antitoxin Mixture 0.1 L+ Non-Sensitizing (Goat).—Each cubic centimeter constitutes a single dose of diphtheria toxin neutralized with the proper amount of antitoxin produced from goats. Marketed in packages of three vials, each containing 1 cc.; in packages of one vial containing 10 cc.; and in packages of one vial containing 30 cc.

TUBERCULINS

Many different methods have been used to prepare from the tubercle bacillus substances which might be used in the diagnosis, treatment or prophylaxis of tuberculosis. These have been, in general, called tuberculins, and a few of the more prominent are enumerated here. For diagnosis, Koch's old tuberculin is almost exclusively employed. For treatment, each tuberculin has its advocates, but it is doubtful whether there is any essential difference in the action of the various forms. The strength varies, however, not only in tuberculins prepared by different methods, but also in different batches prepared in exactly the same manner. When a correct dosage for an individual has been found, therefore, a change to a different laboratory number of the same preparation should be accompanied by a reduction to one half the dose in order to avoid a severe reaction. The plan of treatment provides usually for a gradual increase in dose, keeping the doses low enough to prevent any marked constitutional disturbance. For this reason, the active cooperation of the patient is necessary, and an accurate record must be kept of the temperature and pulse at frequent intervals during the day and of the slightest change in subjective or objective symptoms. The immunity to tuberculin acquired by this increasing dosage is not an immunity to tuberculosis; but the advocates of this tuberculin treatment claim that it frequently is accompanied by clinical improvement. The usual hygienic-dietetic measures should be carried out as well.

Danger from Tuberculins.—The early history of the use of tuberculin is full of instances showing that it is a dangerous substance. The great risk lies in the chance of a severe reaction, and every precaution should be taken, both in diagnosis and in treatment, not to underestimate the patient's susceptibility to the tuberculin. This susceptibility varies enormously in different individuals and at different stages of the treatment, entirely out of relation to the progress of the disease. The use of tuberculin, therefore, requires special knowledge and experience.

TUBERCULIN-KOCH.—Tuberculinum-Koch.—Old Tuberculin.—Concentrated Tuberculin.—Crude Tuberculin.—Koch's original tuberculin is prepared from glycerin bouillon cultures of the tubercle bacillus by evaporating to one-tenth the original volume, sterilizing at 100 C. for one hour, and filtering through a Berkefeld filter. It is a clear brown syrupy liquid, with a high content of glycerin and a characteristic odor.

Actions and Uses.—For diagnosis, old tuberculin may be used by hypodermic injection to show a reaction at the site of application (local), at the site of suspected disease (focal), or generally (constitutional). If positive, the tuberculin reaction merely indicates that the patient has at some time been infected with tuberculosis and not necessarily that he has clinical tuberculosis. In many advanced or acute cases of tuberculosis, the patients do not react, so that the result of a tuberculin test is never absolute but always must be judged in the light of other findings. The occurrence of a focal reaction is good presumptive evidence of an active lesion.

For children, the cutaneous test has been chiefly used. This is performed by abrading the cleansed skin of the forearm in two places, 2 inches (5.08 cm.) apart, through a drop of undiluted old tuberculin at each site; another similar abrasion is used as a control between the two; the two drops of tuberculin are carefully wiped off after ten minutes, allowing no tuberculin to touch the control site. The reaction consists in a zone of redness, usually with a papule, at the point of each tuberculin application, markedly larger than that at the control site. This reaction reaches its height in from twenty-four to forty-eight hours. After infancy an increasing proportion of those who react are found to be free from clinical tuberculosis. The subcutaneous test is used more frequently on adults. A two-hour temperature chart should be kept for two days preceding and two days following each injection. To an adult in good condition, 0.0002 cc. may be given as the initial dose, and, if there is no reaction 0.001 cc. and then 0.005 cc. may be tried. The doses should be given at least three days apart; and if there is the slightest suggestion of a reaction in temperature or symptoms, the dose should be repeated, not increased. Children and weak patients should receive smaller doses, but no very weak patient or one with a fever should be subjected to the danger of a subcutaneous test. A rise of temperature of 1 degree Fahrenheit may be taken as a reaction, especially if accompanied by changes at the site of the disease. This reaction means, just as with the cutaneous test, only infection and not necessarily clinical tuberculosis; and owing to the danger of large doses, patients may fail to react because, though sensitive to tuberculin, they are not sensitive to doses small enough to be used safely.

For treatment, from 0.00000001 to 0.000001 cc. may be used as the initial dose, and not more than two doses a week should be given.

Cutter Laboratory, Berkeley, Calif.

Tuberculin for the Cutaneous Reaction (Pirquet's Reaction).—Marketed in packages containing three capillary tubes.

Tuberculin Old (Tuberculin O. T.).—Marketed in 1 cc. vials of concentrated tuberculin; also in serial dilutions, ranging from 0.01 to 100 mg. per cubic centimeter.

Tuberculin O. T. Bovine.—Made by the same process as the foregoing, except that the organism used is of the bovine type.

The Gilliland Laboratories, Inc., Marietta, Pa.

Original Tuberculin, "O. T."—Marketed in 1 cc. and 3 cc. vials.

Tuberculin "O. T." (Old Tuberculin).—Marketed in packages containing a stated amount of tuberculin with 10 cc. of diluent, so that 1 cc.

represents: No. 1 Dilution (each cubic centimeter equals 0.01 mg.); no. 2 Dilution (each cubic centimeter equals 0.1 mg.); no. 3 Dilution (each cubic centimeter equals 10 mg.); no. 5 Dilution (each cubic centimeter equals 100 mg.). Supplied only on orders direct from laboratories.

Tuberculin Ointment in Capsules (for the Moro Percutaneous Diagnostic Test).—An ointment consisting of tuberculin "Old" and anhydrous wool fat equal parts. Marketed in capsules sufficient for one test.

Pirquet Test.—Old tuberculin in capillary tubes, each sufficient for one test. Marketed in packages of one, five and ten tubes; also in ampules of 1 cc. and 3 cc.

Lederle Antitoxin Laboratories, New York.

Intracutaneous Tuberculin for the Mantoux Test.—Marketed in packages of one vial containing tuberculin "O. T." accompanied by a vial containing physiological solution of sodium chloride sufficient to make 1 cc.; when mixed, the content of the two vials represents 0.001 Gm. of tuberculin.

Tuberculin Subcutaneous Test ("T. O.").—Marketed in vials containing 1 cc.

Tuberculin Pirquet Test ("T. O.").—Old tuberculin marketed in packages containing three collapsible wax tubes and three scarifiers; in packages containing ten capillary tubes and in packages containing twenty-five capillary tubes.

Tuberculin "O. T." (Old Tuberculin).—Marketed in packages containing a stated amount of tuberculin with sufficient diluent to make 1 cc., as follows: Dilution A, containing 0.1 cc.; Dilution B, containing 0.01 cc.; Dilution C, containing 0.001 cc.; Dilution D, containing 0.0001 cc.; Dilution E, containing 0.00001 cc., and Dilution F, containing 0.000001 cc.

Eli Lilly & Company, Indianapolis.

Pirquet Test.—Old tuberculin marketed in packages of three capillary tubes, each tube containing sufficient material for one test.

Tuberculin Ointment for the Moro Percutaneous Test.—Marketed in collapsible tubes containing 2 Gm. of an ointment consisting of equal parts of tuberculin "Old" and hydrous wool fat.

Old Tuberculin, Human Strain, Concentrated.—Marketed in 1 cc. vials for making dilutions for therapeutic use or for making the subcutaneous diagnostic test. Each cubic centimeter equals 1 Gm. of tuberculin.

H. K. Mulford Company, Philadelphia.

Tuberculin "Old" (O. T.).—Marketed in packages of 1 cc. vials (*M 210-026*); also in serial dilutions in five vials of 8 cc. each, the first (*M 231-027*) containing 0.001 mg. in each 2 minims, and each succeeding dilution (*M 231-027* to *M 235-027*, inclusive) being ten times stronger than the preceding.

Dosage.—Two minims.

Pirquet Test for Tuberculosis.—Old tuberculin marketed in capillary tubes, put up in packages of, respectively, one (*M 227-046*), three (*M 227-047*) and ten (*M 227-048*) tubes, each tube containing old tuberculin sufficient for one test, together with packages containing an equal number of tubes of concentrated glycerin bouillon for use as a control.

Pirquet Test for Tuberculosis (Bovine Type).—Old tuberculin (bovine type) marketed in capillary tubes, put up in packages, respectively, of one tube (M 228-046), two tubes (M 228-047), and ten tubes (M 228-048); a corresponding number of tubes containing concentrated glycerin bouillon for use as a control is included in each package.

Tuberculin Ointment (Moro Ointment).—An ointment (*M 340-049*) consisting of 50 per cent of tuberculin "Old" with an equal part of adeps lanae hydrosus.

Tuberculin Ointment (Moro Ointment) (Bovine Type).—An ointment (M 341-049) containing 50 per cent of tuberculin "Old" (bovine type) with an equal part of hydrous wool fat.

Tuberculin Intracutaneous (Human Type).—Marketed in single packages (M331-050) of one intradermal syringe containing tuberculin old

"O. T.," 0.2 mg. in physiological solution of sodium chloride, 0.05 cc.; in packages (M331-051) of five intradermal syringes each containing tuberculin old "O. T.," 0.2 Mg. in physiological solution of sodium chloride, 0.05 cc.

Tuberculin Intracutaneous (Bovine Type).—Marketed in single packages (M 332-050) of one intradermal syringe containing tuberculin old "O. T." (bovine type), 0.2 mg. in physiological solution of sodium chloride, 0.05 cc.; in packages (M 332-051) of five intradermal syringes each containing tuberculin old, "O. T." (bovine type), 0.2 mg. in physiological solution of sodium chloride; and in single vial packages (M 332-028) containing old tuberculin "O. T." (bovine type), 0.012 Gm. in physiological solution of sodium chloride, 3 cc. (sufficient for 50 tests).

Parke, Davis & Company, Detroit.

Tuberculin "Old" (Koch).—Marketed in 1 cc. bulbs (Bio. 491).

Tuberculin for the Ophthalmo-Reaction.—Prepared by precipitating concentrated tuberculin with alcohol. Each disk contains 3.3 mg. of tuberculin, which, when dissolved in 0.3 cc. (5 minims) of water, makes a 1 per cent solution; marketed in tubes containing twelve disks each (*Bio. 460*).

Tuberculin (Old) and Control for the Pirquet Test.—Marketed in packages (*Bio. 530*) containing three sealed glass tubes of tuberculin, each tube containing tuberculin sufficient for one test, and three tubes of control material.

Tuberculin Ointment for the Moro Test.—Marketed in collapsible tubes (*Bio. 520*) containing 2 Gm. of an ointment consisting of 50 per cent of tuberculin-Koch and 50 per cent of anhydrous wool fat.

NEW TUBERCULIN-T. R.—Tuberculinum Novum-T. R. —Tuberkelbacillin Rest, Koch.—Tuberculin Residue.—Tuberculin Rückstand.—This is made from living dried tubercle bacilli by thorough grinding, suspension in water and centrifuging. The supernatant fluid, containing extractives, is discarded and the sediment reground, suspended in a little water and recentrifuged. The fluid is kept this time, while the sediment is reground, suspended and centrifuged as before. This is repeated until practically no sediment remains, when all the fluid portions which have been set aside are combined and diluted with 20 per cent glycerin solution to make the final (standard) product contain the residue of 10 mg. of dried tubercle bacilli in each cubic centimeter of fluid.

New tuberculin is an uncolored, slightly opalescent liquid. It is used occasionally in the treatment of tuberculosis.

H. K. Mulford Company, Philadelphia.

Tuberculin T. R.—Marketed in packages of 1 gram vials (*M221-026*); also in serial dilutions of six graduated strengths (*M291-027* to *M296-027*, inclusive).

Parke, Davis & Company, Detroit.

Tuberculin T. R.—The concentrated product is marketed in single 1 cc. bulbs containing 1 mg. of tubercle solids per cubic centimeter (*Bio. 510*). The dilute product is marketed in packages of six 1 cc. bulbs containing 0.001 mg. of tubercle solids per cubic centimeter (*Bio. 500*).

NEW TUBERCULIN, B. E.—Tuberculinum Novum B. E. —Bazillenemulsion, Koch.—Bacilli Emulsion.—Bacilli emulsion is practically a bacterial vaccine. It is made by suspending one part of pulverized tubercle bacilli in 100 parts of distilled water and 100 parts of glycerin. This mixture stands one day and is then decanted from the grosser particles which have settled. One cubic centimeter thus corresponds to 5 mg. of tubercle bacilli.

It is a white, fairly permanent emulsion, but should be shaken thoroughly before making dilutions. New tuberculin, B. E., is used in the therapeutics of tuberculosis probably more frequently than any other tubercle preparation.

The Gilliland Laboratories, Inc., Marietta, Pa.

Bacillen Emulsion Tuberculin, "B. E."—Marketed in 1 cc. and 3 cc. vials. Ampules containing 10 cc. of dilute Bacillen Emulsion Tuberculin, "B. E.," are supplied on special order only, as dilute tuberculin is not considered a staple product. Dilutions supplied are: no. 1 Dilution (each cubic centimeter equals 0.001 mg.); no. 2 Dilution (each cubic centimeter equals 0.01 mg.); no. 3 Dilution (each cubic centimeter equals 0.1 mg); no. 4 Dilution (each cubic centimeter equals 1.0 mg.); no. 5 Dilution (each cubic centimeter equals 10 mg.); no. 6 Dilution (each cubic centimeter equals 100 mg.).

Lederle Antitoxin Laboratories, New York.

Tuberculin "B. E." (Bacillus Emulsion).—Marketed in vials containing 1 cc.; also in packages containing a stated amount of tuberculin with sufficient diluent to make 1 cc., as follows: Dilution A, containing 0.1 cc.; Dilution B, containing 0.01 cc.; Dilution C, containing 0.001 cc.; Dilution D, containing 0.0001 cc.; Dilution E, containing 0.00001 cc., and Dilution F, containing 0.000001 cc.

H. K. Mulford Company, Philadelphia.

Bacillen Emulsion "B. E."—Marketed in packages of 1 cc. vials (*M244*); also in serial (six) dilutions (*M271* to *M276*, inclusive).

Parke, Davis & Company, Detroit.

Tuberculin B. E. (concentrated).—Bacillus emulsion, marketed in bulbs containing 1 mg. of dry tubercle solids per cubic centimeter (*Bio. 470*).

NEW TUBERCULIN B. E. DRIED.—Tuberculinum Novum B. E. Siccum.—A solution of this is practically a bacterial vaccine. The bacteria are dried, ground for several months in a ball mill, the finely disintegrated bacillary bodies are mixed with a suitable base, similar to that employed for an ordinary hypodermic tablet. The diluent is adjusted so that each tablet represents a definite amount of New Tuberculin B. E. Dried.

Parke, Davis & Company, Detroit.

Tablets Tuberculin B. E.-P. D. & Co. — Marketed in vials no. 1 (*Bio. 474*) of ten tablets, each tablet containing 0.0001 mg. New Tuberculin B. E. Dried; in vials no. 2 (*Bio. 475*) of ten tablets, each tablet containing 0.001 mg. New Tuberculin B. E. Dried; in vials no. 3 (*Bio. 476*) of ten tablets, each tablet containing 0.01 mg. New Tuberculin B. E. Dried; in vials no. 4 (*Bio. 477*) of ten tablets, each tablet containing 0.1 mg. New Tuberculin B. E. Dried; in vials no. 5 (*Bio. 478*) of ten tablets, each tablet containing 1 mg. New Tuberculin B. E. Dried; also marketed in packages (*Bio. 473*) of 5 vials, nos. 1, 2, 3, 4 and 5, inclusive.

NEW TUBERCULIN T. R. DRIED.—Tuberculinum Novum T. R. Siccum.—Tuberculin Residue (Dried).—The mass culture of tubercle bacteria is washed repeatedly, agitated again in water, washed, ground to complete disintegration, extracted repeatedly with water, and the water insoluble material, instead of being ground to form a suspension in water as in the case of the New Tuberculin T. R. Liquid, is dried. The dried sediment is thoroughly mixed with a suitable diluent similar to that used for hypodermic tablets, so that each tablet represents a definite amount of the dry tubercle bacilli.

Parke, Davis & Company, Detroit.

Tablets Tuberculin T. R.-P. D. & Co.—Marketed in vials no. 1 (*Bio. 504*) of ten tablets, each tablet containing 0.0001 mg. New Tuberculin T. R. Dried; in vials no. 2 (*Bio. 505*) of ten tablets, each tablet containing 0.001 mg. New Tuberculin T. R. Dried; in vials no. 3 (*Bio. 506*) of ten tablets, each tablet containing 0.01 mg. New Tuberculin T. R. Dried; in vials no. 4 (*Bio. 507*) of ten tablets, each tablet containing 0.1 mg. New Tuberculin T. R. Dried; in vials no. 5 (*Bio. 508*) of ten tablets, each tablet containing 1 mg. New Tuberculin T. R. Dried; also marketed in packages (*Bio. 503*) of 5 vials, nos. 1, 2, 3, 4 and 5, inclusive.

TUBERCULIN DENYS.—Tuberculinum Denys.—Tuberculine Bouillon Filtré.—Bouillon Filtrate Tuberculin.—This is prepared like old tuberculin, without the prolonged heating and concentration; that is, it is simply a glycerin-broth culture of the tubercle bacillus, passed through a porcelain filter. It contains all the soluble products of the growth of the tubercle bacillus.

The Cutter Laboratory, Berkeley, Calif.

Tuberculin B. F. (Bouillon Filtrate).—Marketed in 1 cc. vials; preserved with cresol; for use in dilutions only. Also in serial dilutions.

The Gilliland Laboratories, Inc., Marietta, Pa.

Bouillon Filtrate Tuberculin, "B. F."—Marketed in 1 cc. and 3 cc. vials; also in packages containing a stated amount of tuberculin with 10 cc. of diluent so that each cubic centimeter represents: no. 1 Dilution (each cubic centimeter equals 0.001 mg.); no. 2 Dilution (each cubic centimeter equals 0.01 mg.); no. 3 Dilution (each cubic centimeter equals 0.1 mg.); no. 4 Dilution (each cubic centimeter equals 1.0 mg.); no. 5 Dilution (each cubic centimeter equals 10 mg.); no. 6 Dilution (each cubic centimeter equals 100 mg.); supplied only on orders direct from laboratories. Preserved with 0.4 per cent cresol.

Lederle Antitoxin Laboratories, New York.

Tuberculin "B. F." (Bouillon Filtrate).—Marketed in vials containing 1 cc.; also in packages containing a stated amount of tuberculin with sufficient diluent to make 1 cc. as follows: Dilution A, containing 0.1 cc.; Dilution B, containing 0.01 cc.; Dilution C, containing 0.001 cc.; Dilution D, containing 0.0001 cc.; Dilution E, containing 0.00001 cc., and Dilution F, containing 0.000001 cc.

H. K. Mulford Company, Philadelphia.

Tuberculin Filtrate, "B. F.," Denys.—Marketed in packages of 1 cc. vials (*M215-026*); also in serial (five) dilutions (*M251-027* to *M255-027*, inclusive).

Parke, Davis & Company, Detroit.

Tuberculin B. F. (Human).—A tuberculin Denys prepared with human cultures bacterium tuberculosis, containing 0.4 per cent of cresol. Marketed in packages of six 1 cc. rubber-stoppered bulbs (*Bio. 480*).

Tuberculin B. F. (Bovine).—A tuberculin Denys prepared with bovine cultures bacterium tuberculosis, containing 0.4 per cent of kresol. Marketed in packages of six 1 cc. rubber-stoppered glass tubes (Bio. 485).

BACTERIAL TOXIN

SCARLET FEVER STREPTOCOCCUS TOXIN.—The toxin is used for active immunization. For this purpose it is injected subcutaneously at weekly intervals. The amount of toxin necessary for immunity production varies with the individual. From three to five doses are given, beginning with 250 to 500 skin test doses for the first injection and increasing the amount of toxin in each subsequent injection. Immunity to the toxin appears in a few weeks and is determined by the reaction to the intracutaneous test.

Parke, Davis & Company, Detroit.

Scarlet Fever Streptococcus Toxin for Preventive Immunization-P. D. & Co.—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in packages of five vials of toxin (Bio. 157) containing, respectively, 500, 2,000, 8,000, 25,000 and 80,000 skin test doses; in packages of fifty vials of toxin (Bio. 158), ten containing 500 skin test doses, ten containing 2,000 skin test doses, ten containing 8,000 skin test doses, ten containing 25,000 skin test doses, and ten containing 80,000 skin test doses.

E. R. Squibb & Sons, New York

Scarlet Fever Streptococcus Toxin-Squibb.—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in packages of five vials of toxin containing, respectively, 500, 2,000, 8,000, 25,000 and 80,000 skin test doses; in packages of fifty vials of toxin, ten containing 500 skin test doses, ten containing 2,000 skin test doses, ten containing 8,000 skin test doses, ten containing 25,000 skin test doses, and ten containing 80,000 skin test doses.

Modified Bacterial Toxin

DIPHTHERIA TOXOID.—Diphtheria Anatoxin.—The toxin of diphtheria modified by the method of Ramon. The work of Ramon, of Glenny, and of their co-workers has shown that the toxin of diphtheria may be modified by treatment with formaldehyde to reduce its toxicity while preserving its antigenic properties.

Action, Uses and Dosage.—Diphtheria toxoid is used for active immunization against diphtheria. It is administered subcutaneously, preferably between the shoulders, in two doses of 1 cc. each, with an interval of three weeks between doses. Since some local and general reactions have been observed in adults and in children over 8 years of age, a test dose of 0.1 cc. of the toxoid diluted with salt solution (1 in 20) should be given to determine susceptibility in such persons.

Cutter Laboratory, Berkeley, Calif.

Diphtheria Toxoid-Cutter.—Prepared from diphtheria toxin whose L+ dose is 0.2 cc. or less by treatment with 0.3 to 0.4 per cent formaldehyde at a temperature of from 37 to 40 C. until its toxicity is so reduced that injection of five maximum human doses into guinea-pigs causes no local or general symptoms of diphtheria poisoning. The product is tested for antigenic potency by injection into at least ten guinea-pigs of one human dose each; if at the end of thirty days at least 80 per cent of the animals survive the injection of five minimum lethal doses of diphtheria toxin, the toxoid is considered satisfactory. Diphtheria toxoid-Cutter is standardized to contain in 3 cc. enough of the toxoid for one immunization treatment. It is marketed in packages of one immunization treatment of three 1 cc. vials; in packages of ten immunization treatments of thirty 1 cc. vials; also in packages of one 30 cc. ampule.

H. K. Mulford Co., Philadelphia.

Diphtheria Toxoid.—Prepared from broth cultures of diphtheria toxin having an L+ dose of 0.25 cc. or less, diluted with physiologic solution of sodium chloride and free of serum proteins. Diphtheria toxin is treated with formaldehyde at a temperature of from 30 to 40 C. until its toxicity is so reduced that 5 cc. will not cause acute death in a guinea-pig. It is tested for antigenic power by injecting guinea-pigs with varying doses and testing the resistance of these guinea-pigs to 5 fatal doses of diphtheria toxin given 30 days after the dose of toxoid. The dose which induces sufficient antigenic response to assure survival of 80 per cent of these animals is the lowest permissible human dose. The finished product contains one such dose per cubic centimeter. It must be so free from toxicity that 5 human doses cause no symptoms of poisoning in a guinea-pig. It is marketed in packages of one immunizing treatment containing a 1 cc. vial of diluted diphtheria toxoid for the reaction test and two 1 cc. vials of diphtheria toxoid; and in packages of ten immunizing treatments containing two 1 cc. vials of diluted diphtheria toxoid for the reaction test and twenty 1 cc. vials of diphtheria toxoid; also in packages of one 30 cc. vial of diphtheria toxoid.

The National Drug Co., Philadelphia.

Diphtheria Toxoid.—Prepared from seven day cultures of the diphtheria bacillus that yield a toxin having an L+ dose of not less than 0.25 cc. The toxin is treated with formaldehyde until its toxicity is so reduced that five human doses will cause no local or general symptoms of diphtheria poisoning when injected subcutaneously into guinea-pigs. The product is tested for antigenic potency by injection subcutaneously of one human dose of the toxoid into each of at least ten guinea-pigs weighing between 270 and 320 Gm.; at the end of thirty days the animals are injected subcutaneously with five minimum lethal doses of a stable diphtheria toxin; 80 per cent of the animals must survive. It is marketed in packages of one immunization treatment, consisting of 3 vials, each containing one human dose; in packages of fifteen immunization treatments, consisting of 45 vials, each containing one human dose; and in packages of 1 vial, containing forty-five human doses. The immunization treatment consists of three doses of 0.5 cc. each of the toxoid, given at intervals of three weeks.

Parke, Davis & Co., Detroit.

Diphtheria Toxoid.—Prepared from diphtheria toxin of which the L+ dose is 0.25 cc. The toxin is treated with formaldehyde according to the specifications of the U. S. Public Health Service until it is detoxified so that 5 cc. (5 minimum human doses) injected into 300 gram guinea-pigs will not produce signs of toxic poisoning. It is tested for antigenic power by subcutaneous injection of 0.5 cc. into ten 300 gram guinea-pigs. After thirty days the animals are injected with 5 M. L. D. of diphtheria toxin and the product is considered satisfactory if 80 per cent survive. Diphtheria toxoid-P. D. & Co. is marketed in packages (Bio 2100) containing one bulb (0.5 cc.) of dilute diphtheria toxoid for the reaction test and two bulbs (0.5 and 1.0 cc., respectively) of diphtheria toxoid; also in hospital packages (Bio 2102) containing two bulbs of dilute diphtheria toxoid for the reaction test (0.5 cc. each) and twenty bulbs of diphtheria toxoid (ten of 0.5 cc. and ten of 1.0 cc.)

Dosage.—For the reaction test, 0.1 cc. of dilute diphtheria toxoid intradermally; for immunization, two doses (0.5 and 1.0 cc.) of the diphtheria toxoid subcutaneously, with an interval of three or four weeks between injections.

E. R. Squibb & Sons, New York.

Diphtheria Toxoid-Squibb.—Prepared from diphtheria toxin by treatment with formaldehyde as prescribed by the U. S. Public Health Service to secure detoxification, which is tested by injection of five maximum human doses into guinea-pigs weighing 300 grams. The product is tested for antigenic potency by injection into at least ten guinea-pigs of one human dose each; if at the end of thirty days at least 80 per cent of the animals survive the injection of five minimum lethal doses of diphtheria toxin, the toxoid is considered satisfactory. Diphtheria toxoid-Squibb is standardized to contain in 2 cc. enough of the toxoid for one immunization treatment. It is marketed in packages of one immunization treatment containing one 1 cc. ampule of diluted diphtheria toxin for the reaction test and two 1 cc. ampules of diphtheria toxoid for treatment; also in packages of one 30 cc. vial of diphtheria toxoid.

BACTERIAL VACCINES

Bacterial vaccines, or bacterins, are suspensions of killed bacteria in physiologic saline solution, usually with the addition of some preservative such as trikresol, phenol or glycerin.

The therapeutic use of stock bacterial vaccines rests on uncertain clinical evidence—the favorable reports should be viewed with recognition of the perhaps unconscious bias to which some users of new remedies are prone. No marked and uniform beneficent results have been authoritatively confirmed.

The dosage and intervals for bacterial vaccine treatment cannot be stated definitely. In general, the severer the disease, the smaller the dose should be; and the smaller the doses, the shorter the intervals. In mild affections no improvement may result until the vaccine is pushed to a systemic reaction.

Prophylactically, the typhoid and paratyphoid vaccines have proved of great value. Plague and cholera vaccines are also used in prophylaxis.

ACNE BACILLUS VACCINE.—Vaccinum Acne.—Prepared from the acne bacillus of Unna and Sabouraud.

Actions and Uses.—The acne bacillus is not found in all cases of acne; but in those cases in which the bacillus is found *(acne vulgaris)* it seems to be the active pathogenic agent and the use of acne vaccine may give good results, especially in the cystic form and in acne indurata. In other cases, the *staphylococcus* is responsible for the inflammation, and the corresponding staphylococcus vaccine may be tried.

The Cutter Laboratory, Berkeley, Calif.

Acne Bacillus Vaccine.—Each cubic centimeter contains 50 million killed acne bacilli suspended in physiological solution of sodium chloride. Marketed in 5 cc. vial packages.

Dosage.—From 5 to 50 million killed bacteria.

Hollister-Stier Laboratories, Spokane, Washington.

Acne Bacillus Vaccine.—A suspension of killed acne bacilli in physiological solution of sodium chloride containing 0.3 per cent of cresol as preservative. Marketed in packages of one 5 cc. vial, each cubic centimeter containing 200 million killed bacteria; in packages of one 20 cc. vial, each cubic centimeter containing 200 million killed bacteria.

Lederle Antitoxin Laboratories, New York.

Acne Vaccine.—Marketed in packages of four vials, containing, respectively, 5, 10, 20 and 40 million killed acne bacilli; in packages of four syringes, containing, respectively, 5, 10, 20 and 40 million killed acne bacilli; in packages of one 5 cc. vial containing 40 million killed acne bacilli per cubic centimeter; in packages of one 10 cc. vial containing 40 million killed acne bacilli per cubic centimeter; in packages of one 20 cc. vial containing 40 million killed acne bacilli per cubic centmeter.

H. K. Mulford Company, Philadelphia.

Acne Bacterin.—Marketed in packages of four syringes (*M 151-0*), containing, respectively, 25 million, 50 million, 100 million and 200 million killed acne bacilli; also marketed in 5 cc. vials (*M 151-9*), containing 200 million killed bacilli per cubic centimeter; in 5 cc. vials containing 25 million killed bacteria per cubic centimeter; in 5 cc. vials containing 200 million killed bacteria per cubic centimeter, and in 20 cc. vials containing 50 million killed bacteria per cubic centimeter.

Dosage.—Initially, from 5 to 25 million.

E. R. Squibb & Sons, New York.

Acne Vaccine.—Marketed in packages of four syringes containing, respectively, 250, 500, 750 and 1,000 million killed bacilli; in packages of four ampules containing, respectively, 250, 500, 750 and 1,000 million killed bacilli (with a syringe); in vials of 5 cc., 10 cc. and 20 cc., each cubic centimeter containing 1,000 million killed bacilli.

United States Standard Products Company, Woodworth, Wis.

Acne Vaccine.—Marketed in packages of one 10 cc. vial, each cubic centimeter containing 40 million killed bacteria, suspended in physiological solution of sodium chloride and preserved with 0.5 per cent of phenol.

CHOLERA VACCINE.—Vaccinum Cholerae.—Prepared from killed cholera vibrios.

Actions and Uses.—Cholera vaccine has been used as a prophylactic with favorable results reported.

Lederle Antitoxin Laboratories, New York.

Cholera Vaccine (Prophylactic).—Marketed in packages of two 1 cc. vials containing, respectively, 4,000 and 8,000 million killed cholera vibrios; also in packages of two 10 cc. vials containing, respectively, 4,000 and 8,000 million killed cholera vibrios per cubic centimeter.

Eli Lilly & Company, Indianapolis.

Cholera Vaccine, Prophylactic.—Marketed in packages of three 1 cc. vials, one containing 500 million killed cholera vibrios per cubic centimeter, and the second and third each containing 1,000 million killed cholera vibrios per cubic centimeter; in packages of ten 2.5 cc. vials each containing 1,000 million killed cholera vibrios per cubic centimeter.

H K. Mulford Company, Philadelphia.

Cholera Bacterin (Cholera Vaccine).—Marketed in packages of three syringes each, the first containing 500 million killed cholera vibrios, while the second and third each contains 1,000 million killed vibrios; also marketed in packages of one 20 cc. vial (M155-4) containing 1,000 million killed cholera vibrios per cubic centimeter.

PERTUSSIS BACILLUS VACCINE.—Vaccinum Pertussis.—Made from the bacillus of whooping cough, isolated first by Bordet and Gengou.

Actions and Uses.—The evidence indicating that it is of value both for prevention and treatment is questionable, and the reports are conflicting, but generally favorable.

Cook Laboratories, Inc., Chicago.

Whooping Cough Vaccine X Plain.—A suspension of killed *Bacillus pertussis* in physiological solution of sodium chloride, preserved with 0.4 per cent of cresol. Marketed in single 1 cc. carpule (tube) packages containing 2,000 million killed bacteria per cubic centimeter and in packages of ten 1 cc. carpules, each containing 2,000 million killed bacteria per cubic centimeter.

The Cutter Laboratory, Berkeley, Calif.

Special Pertussis Vaccine.—Marketed in packages of one 5 cc. vial containing 7,500 million killed pertussis bacilli per cubic centimeter (sterile beads are included to facilitate breaking the tenacious lumps).

The Gilliland Laboratories, Inc., Marietta, Pa.

Pertussis Bacillus Vaccine.—Prepared from several strains of pertussis bacillus grown on blood agar. The killed bacterial emulsion is suspended in physiological solution of sodium chloride; cresol, 0.25 per cent, is added as a preservative. Marketed in packages of four syringes containing 250, 500, 1,000 and 2,000 million killed bacteria, respectively; in packages of four ampules containing 250, 500, 1,000 and 2,000 million killed bacteria, respectively; also in 10 cc. vials containing 2,000 million killed bacteria per cubic centimeter.

Hollister-Stier Laboratories, Spokane, Washington.

Pertussis Bacillus Vaccine.—A suspension of several strains of killed pertussis bacilli in physiological solution of sodium chloride containing 0.3 per cent of cresol as preservative. Marketed in packages of one 5 cc. vial, each cubic centimeter containing 2,000 million killed bacteria; in packages of one 20 cc. vial, each cubic centimeter containing 2,000 million killed bacteria.

Lederle Antitoxin Laboratories, New York.

Pertussis Glycerol-Vaccine-Lederle.—A suspension of killed pertussis bacteria of eight strains in a vehicle composed of glycerol, 66 per cent, physiological solution of sodium chloride, 33 per cent, and cresol, 1 per cent. The product is supplied in packages of five vials containing the glycerol-vaccine and of five vials of sterile diluent with which to make the proper dilution of the vaccine at the time of injection. Each dose consists of 0.1 cc. of pertussis glycerol-vaccine (the concentration of the killed bacteria increases progressively for each respective dose) and 0.9 cc. of sterile physiological solution of sodium chloride. After dilution, the five different doses contain 1,000 million, 2,000 million, 4,000 million, 6,000 million and 8,000 million killed bacteria, respectively. It is marketed (for prophylaxis) in packages of 3 vials containing 2,000 million, 4,000 million and 4,000 million killed bacteria, respectively; also marketed (for treatment) in packages of five vials containing 1,000 million, 2,000 million, 4,000 million, 6,000 million and 8,000 million killed bacteria, respectively.

Pertussis Vaccine for Prophylaxis. — Marketed in packages of three syringes containing, respectively, 2,000 million, 4,000 million and 4,000 million killed pertussis bacilli; in packages of three vials, containing respectively, 2,000 million, 4,000 million and 4,000 million killed pertussis bacilli; in packages of thirty vials; in packages of one 5 cc. vial containing 4,000 million killed pertussis bacilli per cubic centimeter; in packages of one 20 cc. vial containing 4,000 million killed pertussis bacilli per cubic centimeter.

Pertussis Vaccine for Treatment. — Marketed in packages of four syringes containing, respectively, 500, 1,000, 2,000 and 4,000 million killed pertussis bacilli; in packages of four vials containing, respectively, 500, 1,000, 2,000 and 4,000 million killed pertussis bacilli; in packages of one 5 cc. vial containing 2,000 million killed pertussis bacilli per cubic centimeter; in packages of one 10 cc. vial containing 4,000 killed pertussis bacilli per cubic centimeter; in packages of one 20 cc. vial containing 4,000 million killed pertussis bacilli per cubic centimeter.

Eli Lilly & Co., Indianapolis.

Pertussis Vaccine. — A suspension of killed *Bacillus pertussis* in physiological solution of sodium chloride, preserved with 0.3 per cent of cresol. Marketed in packages of four 1 cc. vials containing, respectively, 250 million, 500 million, 1,000 million and 2,000 million killed bacteria per cubic centimeter; in single 5 cc. vial packages containing 2,000 million killed bacteria per cubic centimeter; in single 5 cc. vial packages containing 5,000 million killed bacteria per cubic centimeter; in single 20 cc. vial packages containing 2,000 million killed bacteria per cubic centimeter; and in packages of four 1 cc. vials, each containing 2,000 million killed bacteria per cubic centimeter.

H. K. Mulford Company, Philadelphia.

Pertussis Bacterin-Mulford.—Marketed in boxes of four syringes containing 250, 500, 1,000 and 2,000 million killed Bordet-Gengou bacilli, and in packages of one 5 cc. vial (*M 174-9*) containing 2,000 million killed pertussis bacilli per cubic centimeter.

The National Drug Co., Philadelphia.

Pertussis Vaccine.—A suspension of killed *Bacillus pertussis* in physiological solution of sodium chloride, preserved with 0.4 per cent cresol. Marketed in packages of one 5 cc. vial containing 4,000 million killed pertussis bacilli per cubic centimeter; in packages of one 15 cc. vial containing 4,000 million killed pertussis bacilli per cubic centimeter; in packages of one 30 cc. vial containing 4,000 million killed pertussis bacilli per cubic centimeter.

Parke, Davis & Co., Detroit, Mich.

Pertussis Vaccine.—Marketed in packages of four 1 cc. bulbs (*Bio. 198*), each cubic centimeter containing 4,000 million killed pertussis bacilli (Bordet) suspended in physiological solution of sodium chloride and preserved with cresol, 0.3 per cent; also marketed in packages of four 1 cc. syringes (*Bio. 200*), in 5 cc. vials (*Bio. 201*) and 20 cc. vials (*Bio. 202*).

Pertussis Immunogen.—A bacterial antigen (ectoantigen) obtained by agitating live pertussis bacilli with physiological solution of sodium chloride and separating the liquid from the organisms; the extract is free or nearly free from bacterial cells and toxin and is preserved with phenol. There is some evidence that this material will yield approximately the same results as the ordinary pertussis bacillus vaccine. Pertussis immunogen is marketed in packages of one 10 cc. vial (*Bio. 315*), each cubic centimeter containing the antigens from 2,000 million of bacteria.

E. R. Squibb & Sons, New York.

Pertussis Vaccine, Immunizing. — Marketed in packages of three syringes containing, respectively, 1,000, 2,000 and 4,000 million killed bacilli; in packages of three ampules containing, respectively, 1,000, 2,000 and 4,000 million killed bacilli.

Pertussis Vaccine, Curative.—Marketed in packages of four syringes containing, respectively, 1,000, 2,000 and 4,000 million killed bacilli; in packages of four ampules containing, respectively, 1,000, 2,000 and 4,000 million killed bacilli; and in vials of 5 cc., 10 cc. and 20 cc., each cubic centimeter containing 4,000 million killed bacilli.

Swan-Myers Company, Indianapolis.

Pertussis Bacterin-Swan-Myers (Prophylactic).—Marketed in 6 and 20 cc. vials, containing in each cubic centimeter 5,000 million killed pertussis bacilli.

United States Standard Products Company, Woodworth, Wis.

Pertussis (Whooping Cough) Vaccine.—Marketed in packages of one 10 cc. vial, each cubic centimeter containing 3,000 million killed pertussis bacilli, suspended in physiological solution of sodium chloride and preserved with 0.5 per cent of phenol.

PLAGUE BACILLUS VACCINE.—Vaccinum Pestis.—Made from *Bacillus pestis.*

Actions and Uses.—Vaccine has been used for the prevention of plague with results that appear to justify its use. No practical application, therefore, has been made of vaccine treatment in plague.

Lederle Antitoxin Laboratories, New York.

Plague Vaccine (Prophylactic).—Marketed in 1 cc. vials containing 5,000 million killed plague bacilli; also in 10 cc. vials containing 5,000 million killed plague bacilli per cubic centimeter.

Eli Lilly & Company, Indianapolis.

Plague Vaccine, Prophylactic.—Marketed (for double vaccinations) in single immunization packages of two 1 cc. vials containing, respectively, 1,000 and 2,000 million killed plague bacilli per cubic centimeter; in packages of ten 1.5 cc. vials containing 2,000 million killed plague bacilli per cubic centimeter; in packages (for single vaccinations) of one 20 cc. vial containing 5,000 million killed plague bacilli per cubic centimeter; in packages of three 1 cc. vials containing 5,000 million killed plague bacilli per cubic centimeter (three immunizations).

H. K. Mulford Company, Philadelphia.

Plague Bacterin.—Marketed as follows: (1) in packages of one 1 cc. vial (*M177-15*—for single vaccination), containing 5,000 million killed plague bacilli; (2) in packages of one 10 cc. vial (*M177-16*—for ten vaccinations), containing 5,000 million killed plague bacilli; (3) in "double vaccination" packages (*M177-17*) of two 1 cc. vials, both doses to be used for one immunization, the first dose containing 1,000 million killed plague bacilli and the second dose containing 2,000 million killed plague bacilli; (4) in "10 double vaccination" packages (*M177-18*) of two 10 cc. vials, both doses to be used for ten immunizations, the first dose containing 1,000 million killed plague bacilli per cubic centimeter and the second dose containing 2,000 million killed plague bacilli per cubic centimeter, and (5) in "three dose" packages (*M177-50*) of three 1 cc. vials, the three doses to be used for immunization, the first dose containing 1,000 million, the second dose containing 2,000 million, and the third dose containing 5,000 million killed plague bacilli.

RICINOLEATED SCARLET FEVER ANTIGEN.—A bacterial vaccine detoxified with sodium ricinoleate according to the method of Dr. W. F. Larson. The work of Larson, Huenekens and Colby (J. A. M. A. **86**:1000 [April 3] 1926) indicates that sodium ricinoleate is an effective agent in detoxifying scarlet fever streptococcus toxins without destroying their antigenic properties. These investigators believe that bacteria which are also detoxified with sodium ricinoleate can be added to produce antibacterial as well as antitoxic immunity. Enough favorable evidence has accumulated to indicate that such a preparation is worthy of clinical trial by physicians.

Actions, Uses and Dosage.—The antigen is used for active immunization against scarlet fever. One dose, 1 cc., is given to children. For adults two doses are given: an initial dose of 0.5 cc., and a second dose, a week later, of 1 cc.

Eli Lilly & Co., Indianapolis.

Ricinoleated Scarlet Fever Antigen Immunizing-Lilly.—Prepared from whole broth cultures of scarlet fever streptococci, containing 1,000 million organisms in each cubic centimeter modified with 2 per cent of sodium ricinoleate; marketed in 1 cc., 5 cc. and 20 cc. vials; manufactured by Eli Lilly & Company, by license of Winford P. Larson, Minneapolis, under U. S. patent 1,621,119 (March 15, 1927; expires 1944).

STAPHYLOCOCCUS VACCINE.—Vaccinum Staphylococcicum.—Made from *Staphylococcus pyogenes-aureus,* from *Staphylococcus pyogenes-albus,* or from *Staphylococcus pyogenes-citreus,* or from all three.

Actions and Uses.—Staphylococcus vaccine is used in carbunculosis, furunculosis, sycosis, and certain cases of acne. An autogenous vaccine is preferable, but if this cannot be made, a stock vaccine can be used with some prospect of success. The forms of acne most likely to respond are characterized by deep-seated pustules, with considerable induration, occurring on the face, chest and back. When the lesions are superficial and indolent, the acne bacillus vaccine may give good results.

Abbott Laboratories, North Chicago, Ill.

Staphylococcus Mixed Bacterin.—Each cubic centimeter contains 4,000 million killed *Staphylococcus albus* and *Staphylococcus aureus* in equal proportions; marketed in single 5 cc. vial packages, in single 20 cc. vial packages, and in packages of six 1 cc. ampules.

Cook Laboratories, Inc., Chicago.

Staphylococcus Vaccine (Combined).—A suspension of killed *Staphylococcus albus* and killed *Staphylococcus aureus* in equal proportions, in physiological solution of sodium chloride, preserved with 0.4 per cent of cresol. Marketed in single 1 cc. carpule (tube) packages containing 2,000 million killed bacteria per cubic centimeter and in packages of ten 1 cc. carpules, each containing 2,000 million killed bacteria per cubic centimeter.

The Cutter Laboratory, Berkeley, Calif.

Staphylococcic Vaccine.—A suspension of strains of *Staphylococcus aureus* and *albus* in physiological solution of sodium chloride, containing about 2,000 million to each cubic centimeter. Marketed in 5 cc. vial packages.

Dosage.—From 100 million to 1,000 million killed bacteria.

The Gilliland Laboratories, Inc., Marietta, Pa.

Staphylococcus Vaccine (Albus and Aureus).—A suspension of *Staphylococcus albus* and *Staphylococcus aureus* in equal proportions, in physiological solution of sodium chloride and preserved with 0.25 per cent of trikresol. Marketed in packages of four syringes containing, respectively, 250, 500, 1,000 and 2,000 million killed bacteria in 1 cc.; also marketed in packages of four ampules containing, respectively, 250, 500, 1,000 and 2,000 million killed bacteria in 1 cc.; also supplied in bulk packages of 10 cc. ampules, containing 2,000 million killed bacteria per cubic centimeter.

Hollister-Stier Laboratories, Spokane, Washington.

Staphylococcus Vaccine (Aureus and Albus).—A suspension of killed *Staphylococcus aureus* and *albus* in equal proportions, in physiological solution of sodium chloride containing 0.3 per cent of cresol as preservative. Marketed in packages of one 5 cc. vial, each cubic centimeter containing 1,000 million killed bacteria; in packages of one 20 cc. vial, each cubic centimeter containing 1,000 million killed bacteria.

Lederle Antitoxin Laboratories, New York.

Staphylococcus Vaccine.—Marketed in packages of four syringes containing, respectively (1), 100 million *Staphylococcus albus*, 100 million killed *Staphylococcus aureus* and 50 million killed *Staphylococcus citreus*, (2), 200 million killed *Staphylococcus albus*, 200 million killed *Staphylococcus aureus* and 100 million killed *Staphylococcus citreus*, (3) 400 million killed *Staphylococcus albus*, 400 million killed *Staphylococcus aureus* and 200 million killed *Staphylococcus citreus*, (4) 800 million killed *Staphylococcus albus*, 800 million killed *Staphylococcus aureus*, and 400 million killed *Staphylococcus citreus;* in packages of four vials containing, respectively (1) 100 million killed *Staphylococcus albus*, 100 million killed *Staphylococcus aureus* and 50 million killed *Staphylococcus citreus*, (2) 200 million killed *Staphylococcus albus*, 200 million killed *Staphylococcus aureus* and 100 million killed *Staphylococcus citreus*, (3) 400 million killed *Staphylococcus albus*, 400 million killed *Staphylococcus aureus* and 200 million killed *Staphylococcus citreus*, (4) 800 million killed *Staphylococcus albus*, 800 million killed *Staphylococcus aureus* and 400 million killed *Staphylococcus citreus;* in packages of one 5 cc. vial containing 800 million killed *Staphylococcus albus*, 800 million killed *Staphylococcus aureus* and 400 million killed *Staphylococcus citreus* per cubic centimeter; in packages of one 20 cc. vial containing 800 million killed *Staphylococcus albus*, 800 million killed *Staphylococcus aureus* and 400 million killed *Staphylococcus citreus* per cubic centimeter.

Staphylococcus Albus Vaccine.—Marketed in packages of one 5 cc. vial containing 2,000 million killed *Staphylococcus albus* per cubic centimeter; in packages of one 20 cc. vial containing 2,000 million killed *Staphylococcus albus* per cubic centimeter.

Staphylococcus Aureus Vaccine, Polyvalent.—Marketed in packages of one 5 cc. vial containing 2,000 million killed *Staphylococcus aureus* per cubic centimeter; in packages of one 20 cc. vial containing 2,000 million killed *Staphylococcus aureus* per cubic centimeter.

Eli Lilly & Co., Indianapolis.

Staphylococcus Vaccine.—A suspension of killed *Staphylococcus albus* and killed *Staphylococcus aureus* in equal proportions, in physiological solution of sodium chloride, preserved with 0.3 per cent of cresol. Marketed in single 5 cc. vial packages containing 4,000 million killed bacteria per cubic centimeter and in single 20 cc. vial packages containing 4,000 million killed bacteria per cubic centimeter.

Staphylococcus Aureus Vaccine.—A suspension of killed *Staphylococcus pyogenes aureus* in physiological solution of sodium chloride, preserved with 0.3 per cent of cresol. Marketed in single 5 cc. vial packages containing 2,000 million killed bacteria per cubic centimeter and in single 20 cc. vial packages containing 2,000 million killed bacteria per cubic centimeter.

The National Drug Co., Philadelphia.

Staphylococcus Vaccine.—A suspension of killed *Staphylococcus albus* and killed *Staphylococcus aureus* in equal proportions, in physiological solution of sodium chloride, preserved with 0.4 per cent cresol. Marketed in packages of one 5 cc. vial containing 2,000 million killed bacilli per cubic centimeter; in packages of one 15 cc. vial containing 2,000 million killed bacilli per cubic centimeter; in packages of one 30 cc. vial containing 2,000 million killed bacilli per cubic centimeter.

Parke, Davis & Company, Detroit.

Furunculosis Vaccine. — Marketed in packages of four 1 cc. bulbs (*Bio. 255*), each containing 2,000 million killed *Staphylococcus aureus* obtained from furuncular lesions; in four 1 cc. syringes (*Bio. 257*), each containing 2,000 million killed staphylococci; also in 5 cc. (*Bio. 258*) and 20 cc. (*Bio. 259*) bulbs, each containing 2,000 million killed staphylococci per cubic centimeter.

Staphylococcus Vaccine (*Combined*).—Marketed in packages of four 1 cc. bulbs (*Bio. 376*), each containing 1,000 million killed *Staphylococcus albus* and 1,000 million killed *Staphylococcus aureus;* also in 5 cc. (*Bio. 390*) and 20 cc. (*Bio. 391*) bulbs, each containing 1,000 million killed *Staphylococcus albus* and 1,000 million killed *Staphylococcus aureus* per cubic centimeter.

E. R. Squibb & Sons, New York.

Staphylococcus Vaccine.—Marketed in packages of four syringes containing, respectively, 250, 500, 750 and 1,000 million killed *Staphylococcus aureus* and *Staphylococcus albus* in equal proportion; in packages of four ampules containing, respectively, 250, 500, 750 and 1,000 million killed *Staphylococcus aureus* and *albus* in equal proportion; and in vials of 5 cc., 10 cc. and 20 cc., each cubic centimeter containing 5,000 million killed *Staphylococcus aureus* and *Staphylococcus albus* in equal proportion.

Swan-Myers Company, Indianapolis.

Staphylococcus Bacterin-Swan-Myers. — Marketed in 6 and 20 cubic centimeter vials, each containing 2,000 million killed organisms per cubic centimeter of the *Staphylococcus epidermidis-albus* type.

Mixed Furunculosis Bacterin-Swan-Myers.— Marketed in 6 and 20 cubic centimeter vials, each cubic centimeter containing 1,000 million killed organisms of *Staphylococcus pyogenes-aureus* and 1,000 million killed organisms of *Staphylococcus pyogenes-albus.*

United States Standard Products Company, Woodworth, Wis.

Staphylococcus Combined Vaccine.—Marketed in packages of one 10 cubic centimeter vial, each cubic centimeter containing 1,000 million killed *Staphylococcus albus* and 1,000 million killed *Staphylococcus aureus* suspended in physiological solution of sodium chloride and preserved with 0.5 per cent of phenol.

TYPHOID VACCINE.—Vaccinum Typhosum.—Made from *Bacillus typhosus.* In some cases *Bacillus paratyphosus* A and *Bacillus paratyphosus* B are used either alone or combined with *Bacillus typhosus,* but usually the three organisms are combined in one vaccine.

Actions and Uses.—Typhoid and paratyphoid vaccines are of recognized utility in the prevention of typhoid and paratyphoid fever. The immunity produced is believed to persist in the majority of cases for two years or longer.

The use of vaccine in the treatment of typhoid fever and of the carrier state has given inconclusive results and is not generally considered of value.

Dosage.—As a preventive, typhoid vaccine should be administered only to healthy persons. The skin should be sterilized with iodine and an initial dose of 500 million bacteria injected, with aseptic precautions. This injection should be followed in from seven to ten days by a second dose of one billion bacteria and a third injection of the same size is given from seven to ten days after the second. In addition, half of these doses of each of the paratyphoid bacteria is employed.

The Abbott Laboratories, North Chicago.

Typhoid Prophylactic.—A suspension made from a single strain, that employed in the U. S. Army. Marketed in packages of three ampules, one containing 500 million, and two 1,000 million killed bacteria each; also in packages of three syringes, one containing 500 million, and two 1,000 million killed bacteria each; also marketed in 5 cc. vials containing 1 billion killed typhoid bacilli per cubic centimeter; in 20 cc. vials containing 1 billion killed typhoid bacilli per cubic centimeter.

Cook Laboratories, Inc., Chicago.

Typhoid Vaccine X Plain.—A suspension of killed *Bacillus typhosus* in physiologic solution of sodium chloride, preserved with 0.4 per cent of cresol. Marketed in single 1 cc. carpule (tube) packages containing 500 million killed bacteria per cubic centimeter; in packages of ten 1 cc. carpules, each containing 500 million killed bacteria per cubic centimeter; in packages of four 1 cc. carpules, each containing 1,000 million killed bacteria per cubic centimeter and in packages of ten 1 cc. carpules, each containing 1,000 million killed bacteria per cubic centimeter.

Typhoid Vaccine XX Combined.—A suspension of killed *Bacillus typhosus*, killed *Bacillus paratyphosus* A and killed *Bacillus paratyphosus* B in physiological solution of sodium chloride, preserved with 0.4 per cent of cresol. Marketed in single 1 cc. carpule (tube) packages containing 500 million killed *Bacillus typhosus*, 375 million killed *Bacillus paratyphosus* A and 375 million killed *Bacillus paratyphosus* B per cubic centimeter; in packages of ten 1 cc. carpules each containing 500 million killed *Bacillus typhosus*, 375 million killed *Bacillus paratyphosus* A and 375 million killed *Bacillus paratyphosus* B per cubic centimeter; in single 1 cc. carpule packages containing 1,000 million killed *Bacillus typhosus*, 750 million killed *Bacillus paratyphosus* A and 750 million killed *Bacillus paratyphosus* B per cubic centimeter and in packages of ten 1 cc. carpules each containing 1,000 million killed *Bacillus typhosus*, 750 million killed *Bacillus paratyphosus* A and 750 million killed *Bacillus paratyphosus* B per cubic centimeter.

The Cutter Laboratory, Berkeley, Calif.

Typhoid Vaccine.—A suspension of killed bacilli in physiological solution of sodium chloride, containing 500 million killed typhoid bacilli of various strains in each cubic centimeter. Marketed in 5 cc. vial packages.

Dosage.—From 5 to 50 million, every three to five days.

Typhoid Prophylactic. — A suspension made from a single strain, namely, that employed by the U. S. Army, containing 1,000 million killed typhoid bacilli per cubic centimeter. Marketed in packages of three bottles, one containing 500 million, and two each 1,000 million typhoid bacilli. Also marketed in packages of one syringe containing 1,000 million killed typhoid bacilli per cubic centimeter and in packages of one 20 cc. bottle containing 1,000 million killed typhoid bacilli per cubic centimeter.

Typhoid-Paratyphoid Prophylactic.—Marketed in packages of three vials, one vial containing 500 million killed typhoid bacilli, 250 million killed paratyphoid A bacilli and 250 million killed paratyphoid B bacilli per cubic centimeter, and two vials each containing 1,000 million killed typhoid bacilli, 500 million killed paratyphoid A bacilli and 500 million killed paratyphoid B bacilli per cubic centimeter; in packages of one 20 cc. vial containing 1,000 million killed typhoid bacilli, 500 million killed paratyphoid A bacilli and 500 million killed paratyphoid B bacilli per cubic centimeter; and in packages of one syringe containing 1,000 million killed typhoid bacilli, 500 million killed paratyphoid A bacilli and 500 million killed paratyphoid B bacilli per cubic centimetetr.

The Gilliland Laboratories, Inc., Marietta, Pa.

Typhoid Vaccine.—Prepared according to the method of the U. S. Army Medical School Laboratory from the Rawling's strain. Marketed in packages containing three syringes, the first containing 500 million killed typhoid bacilli and the second and third containing each 1,000 million killed typhoid bacilli; in packages containing three ampules, the first containing 500 million killed typhoid bacilli, and the second and third containing each 1,000 million killed typhoid bacilli; also in ampules containing 5, 10 and 20 cc. of the vaccine as ordered; also marketed in packages of thirty ampules (ten complete immunizations), ten containing 500 million, and twenty containing 1,000 million killed typhoid bacilli each.

Typhoid-Paratyphoid Bacterial Vaccine Immunizing. — Marketed in packages of three 1 cc. ampules, one containing 250 million each killed paratyphoid A and B, and 500 million killed typhoid bacilli and two containing 500 million each killed paratyphoid A and B and 1,000 million killed typhoid bacilli, suspended in physiological solution of sodium chloride, containing 0.25 per cent of cresol; in packages of three 1 cc. syringes, one containing 250 million each of killed paratyphoid A and B and 500 million killed typhoid bacilli and two containing 500 million each of killed paratyphoid A and B and 1,000 million killed typhoid bacilli, suspended in physiological solution of sodium chloride containing 0.25 per cent of cresol; also marketed in vials containing 5, 10 and 20 cc. of the latter strength; and in hospital size packages of ten complete immunizations. Each immunizing treatment consists of three 1 cc. vials, the first dose containing 500 million killed typhoid bacilli, 250 million killed paratyphoid A bacilli and 250 million killed paratyphoid B bacilli and the second and third each containing 1,000 million killed typhoid bacilli, 500 million killed paratyphoid A bacilli and 500 million killed paratyphoid B bacilli.

Lederle Antitoxin Laboratories, New York.

Typhoid Vaccine (for Prophylactic Treatment).—Marketed in packages of three syringes containing, respectively, 500, 1,000 and 1,000 million killed typhoid bacilli; in packages of three vials containing, respectively, 500, 1,000 and 1,000 million killed typhoid bacilli; in packages of thirty vials; in packages of one 5 cc. vial containing 1,000 million killed typhoid bacilli per cubic centimeter; in packages of one 20 cc. vial containing 1,000 million killed typhoid bacilli per cubic centimeter.

Typhoid Combined Vaccine (Prophylactic).—Marketed in packages of three syringes containing, respectively, (1) 500 million killed typhoid bacilli, 375 million killed paratyphoid bacilli A and 375 million killed paratyphoid bacilli B, (2) 1,000 million killed typhoid bacilli, 750 million killed paratyphoid bacilli A and 750 million killed paratyphoid bacilli B, (3) 1,000 million killed typhoid bacilli, 750 million killed paratyphoid bacilli A and 750 million killed paratyphoid bacilli B; in packages of three vials containing, respectively (1) 500 million killed typhoid bacilli, 375 million killed paratyphoid bacilli A and 375 million killed paratyphoid bacilli B, (2) 1,000 million killed typhoid bacilli, 750 million killed paratyphoid bacilli A and 750 million killed paratyphoid bacilli B, (3) 1,000 million killed typhoid bacilli, 750 million killed paratyphoid bacilli A and 750 million killed paratyphoid bacilli B; in packagegs of thirty vials; in packages of one 5 cc. vial containing 1,000 million killed typhoid bacilli, 750 million killed paratyphoid bacilli A and 750 million killed paratyphoid bacilli B per cubic centimeter; in packages of one 20 cc. vial containing 1,000 million killed typhoid bacilli, 750 million killed paratyphoid bacilli A and 750 million killed paratyphoid bacilli B per cubic centimeter.

Hollister-Stier Laboratories, Spokane, Washington.

Typhoid-Paratyphoid Vaccine (Prophylactic).—A suspension of killed typhoid, paratyphoid A, and paratyphoid B bacilli in physiological solution of sodium chloride containing 0.3 per cent of cresol as preservative. Marketed in packages of one 5 cc. vial, each cubic centimeter containing 1,000 million killed typhoid bacilli and 500 million each of killed paratyphoid A and B bacilli; in packages of one 20 cc. vial, each cubic centimeter containing 1,000 million killed typhoid bacilli and 500 million each of killed paratyphoid A and B bacilli.

Eli Lilly & Company, Indianapolis.

Typhoid Vaccine, Prophylactic and Therapeutic.—A suspension in physiological solution of sodium chloride, containing 0.3 per cent of cresol. Marketed in immunization packages of three 1 cc. vials, one containing 500 million and two containing 1,000 million killed typhoid bacilli each; in three 1 cc. syringes, one containing 500 million and two containing

1,000 million killed typhoid bacilli each; also marketed in hospital size packages of ten complete immunizations in ten 2.5 cc. vials, one vial containing a complete immunization.

Typhoid Mixed Vaccine, Prophylactic and Therapeutic.—A suspension in physiological solution of sodium chloride, containing 0.3 per cent of cresol. Marketed in packages of 5 and 20 cc. vials, each cubic centimeter containing 500 million each killed paratyphoid A and B, and 1,000 million killed typhoid bacilli; in packages of three 1 cc. syringes, one, the first dose, containing 250 million each killed paratyphoid A and B, and 500 million killed typhoid bacilli; two, the second and third doses, containing 500 million each killed paratyphoid A and B, and 1,000 million killed typhoid bacilli; also marketed in hospital size packages of ten complete immunizations in ten 2.5 cc. vials, each vial containing a complete immunization; in packages of three 1 cc. vials; one, the first dose, containing 250 million each killed paratyphoid A and B, and 500 million killed typhoid bacilli; two, the second and third doses, containing 500 million each killed paratyphoid A and B, and 1,000 million killed typhoid bacilli.

H. K. Mulford Company, Philadelphia.

Typho-Bacterin. — Marketed in packages ("immunizing") of three syringes (*M 193-10*) and in packages of three 1 cc. vials (*M 193-50*), containing, respectively, 500 million, 1,000 million and 1,000 million killed typhoid bacilli; also marketed in packages of thirty 1 cc. vials (*M 193-5*) (hospital size), being ten sets of three immunizing doses containing, respectively, 500, 1,000 and 1,000 million killed typhoid bacilli.

Typho-Bacterin Mixed (Triple Vaccine TAB).—Marketed in packages of four 1 cc. syringes (*M 195-0*), the first dose containing 125 million killed typhoid bacteria, 62.5 million killed paratyphoid "A" bacteria and 62.5 million killed paratyphoid "B" bacteria; the second, third and fourth doses containing, respectively, two, four and eight times the number of bacteria in the first dose. Also marketed in 20 cc. vials (*M 195-4*), and in 5 cc. vials (*M 195-9*), containing 1,000 million killed typhoid bacteria, 500 million killed paratyphoid "A" bacteria and 500 million killed paratyphoid "B" bacteria per cubic centimeter. Typhoid-bacterin mixed is also supplied in packages of three syringes (*M 195-10*), in packages of three 1 cc. vials (*M 195-50*), the first dose containing 500 million killed typhoid bacteria, 250 million killed paratyphoid "A" bacteria and 250 million killed paratyphoid "B" bacteria, while the second and third doses contain, respectively, twice the number of bacteria in the first. Also marketed in packages of thirty 1 cc. vials (M 195-5), being ten immunizations of three doses each, the first dose containing 500 million killed typhoid bacilli and 250 million each of killed paratyphoid A and paratyphoid B bacilli, and the second and third doses each containing 1,000 million killed typhoid bacilli and 500 million each of killed paratyphoid A and paratyphoid B bacilli.

The National Drug Co., Philadelphia.

Typhoid Vaccine.—A suspension of killed *Bacillus typhosus* in physiological solution of sodium chloride, preserved with 0.4 per cent cresol. Marketed in packages of one 5 cc. vial containing 1,500 million killed typhoid bacilli per cubic centimeter; in packages of one 15 cc. vial containing 1,500 million killed typhoid bacilli per cubic centimeter; in packages of one 30 cc. vial containing 1,500 million killed typhoid bacilli per cubic centimeter.

Typhoid-Paratyphoid Combined Vaccine. — A suspension of killed *Bacillus typhosus*, killed *Bacillus paratyphosus* A and killed *Bacillus paratyphosus* B in physiological solution of sodium chloride, preserved with 0.4 per cent cresol. Marketed in packages of three 1 cc. vials, the first dose containing 500 million killed typhoid bacilli, 375 million killed paratyphoid A bacilli and 375 million killed paratyphoid B bacilli, the second and third doses each containing 1,000 million killed typhoid bacilli, 750 million killed paratyphoid A bacilli and 750 million killed paratyphoid B bacilli; in packages of one 5 cc. vial containing 1,000 million killed typhoid bacilli, 750 million killed paratyphoid A bacilli and 750 million killed paratyphoid B bacilli per cubic centimeter; in packages of one 15 cc. vial containing 1,000 million killed typhoid bacilli, 750 million killed paratyphoid A bacilli and 750 million killed paratyphoid B bacilli per cubic centimeter; in packages of one 30 cc. vial containing 1,000 million killed typhoid bacilli, 750 million killed paratyphoid A bacilli and 750 million killed paratyphoid B bacilli per cubic centimeter; in packages of ninety 1 cc. vials (thirty immunizations), being thirty sets of three doses, the first dose containing 500 million killed typhoid bacilli and 375 million each of killed paratyphoid A and B bacilli, the second and third doses containing, respectively, twice the number of bacilli in the first dose.

Typhoid-Paratyphoid A Vaccine.—Marketed in packages of one 5 cc. vial containing 750 million killed typhoid bacilli and 250 million killed paratyphoid A bacilli per cubic centimeter; in packages of one 15 cc. vial containing 750 million killed typhoid bacilli and 250 million killed paratyphoid A bacilli per cubic centimeter; in packages of one 30 cc. vial containing 750 million killed typhoid bacilli and 250 million killed paratyphoid A bacilli per cubic centimeter.

Parke, Davis & Company, Detroit.

Typhoid Vaccine (Prophylactic). — Marketed in packages of three ampules *(Bio. 427)*, one containing 500 million, and two, 1,000 million, killed bacteria each; also in packages of three syringes *(Bio. 426)*, one containing 500 million and two, 1,000 million, killed bacteria each; in packages *(Bio. 429)* of thirty ampules, ten containing 500 million, and twenty containing 1,000 killed typhoid bacilli each; also marketed in packages of one 20 cc. vial *(Bio. 431)* containing 1,000 million killed typhoid bacilli per cubic centimeter.

Typhoid-Paratyphoid Vaccine (Prophylactic).—Marketed in packages of three 1 cc. bulbs (Bio. 441), the first dose containing 500 million killed typhoid bacteria, 375 million killed paratyphoid A and 375 million killed paratyphoid B bacteria, the second and third doses each containing 1,000 million killed typhoid bacteria, 750 million killed paratyphoid A and 750 million killed paratyphoid B bacteria, respectively, suspended in physiological solution of sodium chloride and preserved with 0.3 per cent of cresol; also marketed in packages of three 1 cc. syringes (Bio. 443), the first dose containing 500 million killed typhoid bacteria, 375 million killed paratyphoid A and 375 million killed paratyphoid B bacteria, the second and third doses each containing 1,000 million killed typhoid bacteria, 750 million killed paratyphoid A and 750 million killed paratyphoid B bacteria, respectively, suspended in physiological solution of sodium chloride and preserved with 0.3 per cent of cresol; in packages *(Bio. 444)* of thirty ampules, ten containing 500 million killed typhoid bacilli, 375 million killed paratyphoid A and 375 million killed paratyphoid B bacilli, and twenty containing 1,000 million killed typhoid bacilli, 750 million killed paratyphoid A and 750 million killed paratyphoid B bacilli; also marketed in packages of one 20 cc. vial *(Bio. 446)* containing 1,000 million killed typhoid bacilli and 750 million each of killed paratyphoid bacilli A and B per cubic centimeter.

E. R. Squibb & Sons, New York.

Typhoid Vaccine, Curative.—Marketed in packages of four syringes containing, respectively, 250, 500, 750 and 1,000 million killed typhoid bacilli; in packages of four ampules containing, respectively, 250, 500, 750 and 1,000 million killed typhoid bacilli; and in vials of 5 cc., 10 cc. and 20 cc., each cubic centimeter containing 1,000 million killed typhoid bacilli.

Typhoid Vaccine (Immunizing).—Marketed in boxes of three syringes containing 500, 1,000 and 1,000 million killed bacilli; also in boxes of three ampules containing, respectively, 500, 1,000 and 1,000 million killed bacilli, with a syringe; also in hospital size package of thirty ampules, ten containing 500 million and twenty containing 1,000 million killed bacilli.

Typhoid Vaccine Combined, Immunizing.—Marketed in packages of three syringes, one containing 500 million killed typhoid bacilli and 375 million each of killed paratyphoid A and paratyphoid B bacilli, and each of the other two syringes containing 1,000 million killed typhoid bacilli and 750 million each of killed paratyphoid A and paratyphoid B bacilli; in packages of three ampules containing, respectively, the same dosages as the three-syringe package; in packages of 30 ampules, hospital size, 10 of which contain, each, 500 million killed typhoid bacilli and 375 million each of killed paratyphoid A and paratyphoid B bacilli, and 20 of which contain, each, 1,000 million killed typhoid bacilli and 750 million each of killed paratyphoid A and paratyphoid B bacilli; and in vials of 5 cc., 10 cc. and 20 cc., each cubic centimeter containing 2,500 million killed bacilli.

Swan-Myers Company, Indianapolis.

Typhoid Bacterin-Swan-Myers (Prophylactic).—Marketed in 6 and 20 cc. vials, each cubic centimeter containing 1,000 million killed typhoid bacilli.

Typhoid-Paratyphoid Bacterin-Swan-Myers (Prophylactic). — Marketed in packages of three 1 cc. vials, one vial containing 250 million killed typhoid bacilli and 125 million each of paratyphoid bacilli A and B, while the other two vials each contain 500 million killed typhoid bacilli and 250 million each of paratyphoid bacilli A and B; in packages (hospital) of thirty-six ampoules, twelve of which contain 250 million killed typhoid bacilli and 125 million each of paratyphoid bacilli A and B, and twenty-four of which contain 500 million killed typhoid bacilli and 250 million each of paratyphoid bacilli A and B; and in 6 and 20 cc. vials, containing 500 million killed typhoid bacilli, and 250 million each of paratyphoid bacilli A and B in each cubic centimeter.

United States Standard Products Company, Woodworth, Wis.

Typhoid Vaccine.—Marketed in packages of three 1 cc. vials, containing 500 million, 1,000 million and 1,000 million killed typhoid bacteria, respectively, suspended in physiological solution of sodium chloride and preserved with 0.5 per cent phenol.

Typhoid Paratyphoid Vaccine Combined. — Marketed in packages of three 1 cc. vials, the first dose containing 500 million killed typhoid bacteria, 375 million killed paratyphoid A and 375 million killed paratyphoid B bacteria, the second and third doses each containing 1,000 million killed typhoid bacteria, 750 million killed paratyphoid A and 750 million paratyphoid B, suspended in physiological solution of sodium chloride and preserved with 0.5 per cent phenol.

Mixed Bacterial Vaccines

These contain more than one species of bacteria.

Actions and Uses.—The employment of bacterial vaccines should be based either on the discovery of the causative micro-organism by careful bacteriologic examination of the patient under treatment or on well established clinical knowledge which has shown the disease present to be regularly due to the activity of a definite germ. As a rule, one organism plays the predominant role and the destruction of the causative agent will effect a cure. In some cases, however, it has been found that two or more organisms are associated in producing the diseased condition. In such cases, a vaccine containing all the known causative antigens has been thought to be indicated. When this etiologic association has been determined by actual bacteriologic examination, a mixture of two autogenous vaccines or two corresponding stock vaccines may have a logical basis. If the bacteriologic examination is omitted, the mixture rests on a purely hypothetical assumption and the method becomes wholly irrational.

While the subject was still in the earlier experimental stage, various mixtures of vaccine, so-called "mixed" vaccines, were admitted to N. N. R. by the Council. As knowledge concerning the action of these products increased, however, it was found inadvisable, in most instances, to continue recognition of them; and the mixed vaccines, which had been admitted, were deleted unless their usefulness was established by acceptable clinical evidence. New mixed vaccine products are subject to the same conditions before being accepted.

ERYSIPELAS AND PRODIGIOSUS TOXINS (COLEY).—Toxicum Erysipelatis et Toxicum Bacilli Prodigiosi.—This preparation is practically a mixed bacterial vaccine made from strains of *Streptococcus pyogenes* isolated from cases of erysipelas and from *Bacillus prodigiosus.* Its use has been advised in cases of inoperable sarcoma.

Actions and Uses.—This remedy is said to have benefited and produced cures in a small percentage of cases treated, though there is some difference of opinion as to this.

Dosage.—From 0.05 to 0.5 cc. (1 to 8 minims). It is given by hypodermic injection partly into the tumor or its near neighborhood and partly at a distance to secure the benefit of both local and systemic effect. A reaction consisting of chill and rise of temperature is expected to follow the injections, until tolerance becomes established.

Parke, Davis & Company, Detroit.

Erysipelas and Prodigiosus Toxins (Coley). — Marketed in packages containing five 1 cc. bulbs (*Bio. 451*) and in 15 cc. bulbs (*Bio. 455*).

Sensitized Bacterial Vaccines—Serobacterins

These products are prepared in the same manner as bacterial vaccines, except that the bacterial suspensions are treated with the serum of an animal which has been immunized to some extent against the species of organism in hand. The serum is then washed from the bacterial bodies by centrifugation and the latter are resuspended in physiological solution of sodium chloride. This treatment, it is claimed, sensitizes the bacteria so that they are more easily attacked by the protective forces of the patient, cause less reaction, and produce a quicker immunity. It is held that a time-consuming portion of the process of immunity, namely, the formation of specific amboceptors necessary for the breaking up of the bacteria, is dispensed with. These amboceptors, procured from the immunized goat and combined with the bacteria, prepare the bacteria, it is believed, in the same manner as amboceptors formed in the body of the patient; their action, therefore, is said to be more rapid than that of the ordinary bacterial vaccine.

Method of Preparation.—An immune serum is obtained from animals which have been treated by injections of dead, and later, living cultures of bacteria until the blood shows a high titer of specific antibodies (opsonins, agglutinins, etc.). A heavy suspension of bacteria is mixed with a corresponding immune serum. The mixture is kept at laboratory temperature for twenty-four hours, with frequent shaking. During this time, the bacteria and antibodies contained in the immune serum are believed to combine. Sterile saline solution is then added and the mixture centrifugated. The bacteria with the specific antibodies attached are thrown down and the supernatant fluid is removed. The washing is repeated until all traces of free serum are removed. Before sensitization, the bacteria are killed by heat or antiseptics.

H. K. Mulford Company, Philadelphia.

Acne Serobacterin-Mulford (*Sensitized Acne Vaccine, Polyvalent*).—Marketed in packages of four 1 cc. syringes (*M 101-0*), containing, respectively, 100 million, 200 million, 400 million and 800 million killed sensitized bacteria; in 5 cc. vials (*M 101-9*), containing 800 million killed sensitized bacteria per cubic centimeter.

Cholera Serobacterin-Mulford (*Sensitized Cholera Vaccine*).—Marketed in packages of three syringes (*M 105-10*), containing, respectively, 500, 1,000 and 2,000 million killed sensitized cholera vibriones suspended in sterile phyisological solution of sodium chloride.

Staphylo-Serobacterin (*Sensitized Staphylococcic Vaccine*).—Marketed in packages of four syringes (*M 126-0*), containing, respectively, *Staphylococcus aureus* and *Staphylococcus albus* in equal proportions, 500, 1,000, 2,000 and 4,000 million killed sensitized staphylococci; in 5 cc. vials (*M 126-9*), and in single 1 cc. syringes, containing 4,000 million killed sensitized staphylococci per cubic centimeter.

Typho-Serobacterin-Mulford (*Sensitized Typhoid Vaccine*).—Marketed in packages of 5 cc. vials (*M136-9*), each containing 2,000 million killed sensitized typhoid bacilli per cubic centimeter. Also marketed in packages of three syringes, being three immunizing doses, the first containing 1,000 million and the second and third each containing 2,000 million killed typhoid bacilli.

Typho-Serobacterin-Mulford Mixed (*Sensitized Triple Vaccine TAB*).—Marketed in packages of four 1 cc. syringes (*M 138-0*) and in packages of four 1 cc. vials (*M 138-5*), the first dose containing 250 million killed sensitized typhoid bacteria, 125 million killed sensitized paratyphoid "A" bacteria and 125 million killed sensitized paratyphoid "B" bacteria; the second, third and fourth doses contain, respectively, two, four and eight times the number of bacteria in the first dose. Also marketed in 5 cc. vials (*M 138-9*), and in single 1 cc. syringes containing 2,000 million killed sensitized bacteria, 1,000 million killed sensitized paratyphoid "A" bacteria, and 1,000 million killed sensitized paratyphoid "B" bacteria per cubic centimeter, and in packages of three syringes (*M 138-10*) and in packages of three 1 cc. vials (*M 138-50*), the first dose containing 1,000 million killed sensitized typhoid bacteria, 500 million killed sensitized paratyphoid "A" bacteria and 500 million killed paratyphoid "B" bacteria, while the second and third doses contain, respectively, twice the number of bacteria in the first dose; in packages of thirty 1 cc. vials (*M 138-5*) (hospital size), being ten sets of three doses, the first containing 1,000 million killed sensitized typhoid bacilli, and 500 million each of killed sensitized paratyphoid bacilli A and B, the second and third containing, respectively, twice the number of bacilli in the first dose.

IV. Diagnostic Agents

TOXINS FOR IMMUNITY TESTS

DIPHTHERIA IMMUNITY TEST (SCHICK TEST).—This test is intended to determine those persons who have not in the blood an amount of diphtheria antitoxin sufficient to render them immune to diphtheria. The test depends on the phenomenon that, when a small amount of diphtheria toxin is injected intradermally into a person who has no free antitoxin in his blood, a circumscribed area of redness and infiltration from 1 to 2 cm. in diameter develops at the site of injection. Should the patient have free antitoxin in his blood, no reaction occurs. In nonimmune persons, the reaction occurs in from twenty-four to forty-eight hours, and is at its height in from forty-eight to seventy-two hours. It remains for from six to twelve days, is followed by slight scaling, and leaves a brownish, pigmented spot. In some persons, a pseudoreaction may occur, which may be differentiated by its earlier appearance and disappearance, and the facts that it is less circumscribed and is not followed by pigmentation.

The test is of special value in institutions and among groups of persons exposed to diphtheria, in determining which individuals should be given an immunizing dose of diphtheria antitoxin or diphtheria toxin-antitoxin mixture.

Diphtheria toxin in dilute solutions, such as are necessary for the test, soon lose in potency.

Cutter Laboratory, Berkeley, Calif.

Diphtheria Toxin for the Schick Test.—Marketed in packages of two vials, one containing a definite volume of diphtheria toxin and the other containing sterile physiologic solution of sodium chloride with which the toxin is to be diluted before administration. The diluted toxin is of such a strength that 0.1 cc. given intracutaneously constitutes a 1/50 M.L.D. There are approximately 50 test doses in each package.

The Gilliland Laboratories, Inc., Marietta, Pa.

Schick Test.—Marketed in packages containing one vial of diphtheria toxin (standardized) and one 10 cc. vial of physiological solution of sodium chloride for dilution, the amount being sufficient for fifty tests. Two-tenths (0.2) cc. of the dilution is injected intradermally, which represents 1/50 minimum lethal dose for a guinea-pig of 250 gram weight. As a means of control, the Shick test control, representing diphtheria toxin of the same lot heated sufficiently to destroy the specific exotoxins, is supplied.

Lederle Antitoxin Laboratories, New York.

Schick Test.—Marketed in packages of one vial containing diphtheria toxin sufficient for 50 tests; in packages of one vial containing diphtheria toxin sufficient for 100 tests. Each package is accompanied by the required amount of sterile diluent.

Eli Lilly & Company, Indianapolis.

Schick Test.—Marketed in packages containing one vial of diphtheria toxin sufficient for ten tests and a vial of sterile physiological solution of sodium chloride for diluting the toxin to the proper dosage; in packages of two vials, one containing diphtheria toxin sufficient for fifty tests and the other vial containing the proper amount of diluent. Each dose consists of approximately 0.001 cc. of toxin (0.2 cc. of the diluted toxin) which is equivalent to 1/40 of a minimum lethal dose for a guinea-pig of 250 Gm. weight. As a means of control, the Schick test control, representing diphtheria toxin of the same lot heated sufficiently to destroy the specific exotoxins, is supplied.

H. K. Mulford Company, Philadelphia.

Diphtheria Toxin for the Schick Test.—Marketed in packages of two 5 cc. vials (M. 208), one containing undiluted diphtheria toxin and the other containing sufficient sterile solution of sodium chloride for dilution to make 50 doses of 0.1 cc.; also marketed in packages of two 10 cc. vials (M. 213), one containing undiluted diphtheria toxin and the other containing sufficient sterile solution of sodium chloride for dilution to make 100 doses of 0.1 cc. As a means of control the Schick Test Control is supplied in packages of one 5 cc. vial (M. 209-224), containing heated and diluted diphtheria toxin sufficient for at least 50 tests; also in packages of one 10 cc. vial (M. 214), containing heated and diluted diphtheria toxin sufficient for at least 100 tests.

Parke, Davis & Co., Detroit.

Diphtheria Toxin for Schick Test.—Marketed in packages (*Bio. 78*) containing one vial of 0.1 cc. of undiluted, standardized diphtheria toxin, one vial of 5 cc. of sterile physiologic solution of sodium chloride, and one sterile syringe point. The dose is 0.1 cc. of the diluted toxin or 1/50 of the minimum lethal dose of diphtheria toxin for a guinea-pig of 250 Gm. weight: each package, therefore, contains material sufficient for 50 doses. As a means of control, the Control for the Schick Test (*Bio. 79*) representing diluted diphtheria toxin heated sufficiently to destroy the specific erotoxins is supplied.

E. R. Squibb & Sons, New York.

Diphtheria Immunity Test (Schick Test)-Squibb.—Marketed in packages of one vial containing diphtheria toxin sufficient for fifty tests, accompanied by a vial of the required amount of sterile diluent; also in packages of one syringe containing diphtheria toxin sufficient for 100 tests, accompanied by a vial of the required amount of sterile diluent.

United States Standard Products Company, Woodworth, Wis.

Diphtheria Toxin for Schick Test and Control.—Marketed in packages containing a vial with undiluted diphtheria toxin standardized, and a 2 cc. vial of sterilized physiological solution of sodium chloride with which the toxin is diluted before using. The dose is 0.2 cc.: each package contains, therefore, 10 tests. As a means of control, there is also supplied diphtheria toxin of the same lot but heated sufficiently to destroy the specific exotoxins and 2 cc. of physiological solution of sodium chloride for diluent. The product is marketed in packages containing 5 times the foregoing amount, sufficient for 50 tests and control tests; also marketed in packages sufficient for 100 tests, but the strength of the toxin is such that the dose is 0.1 cc.

SCARLET FEVER IMMUNITY TEST.—The toxin of the hemolytic streptococcus of scarlet fever is used to determine those persons who are susceptible to scarlet fever. The toxin is first carefully standardized on human beings and diluted so that 0.1 cc. represents a skin test dose.

The test dose is injected intracutaneously on the forearm and the degree of susceptibility is determined at the end of from twenty-two to twenty-four hours. An area of reddening 1 cm. or more in diameter constitutes some degree of a positive reaction, while a smaller area of reddening is considered negative. Reactions which have appeared but which have entirely faded at the end of twenty-four hours are regarded as negative. Positive reactions fade rapidly and have usually disappeared at the end of from forty-eight to seventy-two hours.

Scarlet fever streptococcus toxin diluted for use will retain its potency for at least two months at room temperature.

Parke, Davis & Company, Detroit.

Scarlet Fever Streptococcus Toxin for Skin Test-P. D. & Co.—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in single 1 cc. vial packages (Bio. 154) containing sufficient toxin for ten tests.

E. R. Squibb & Sons, New York.

Scarlet Fever Streptococcus Toxin for Dick Test-Squibb.—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in packages of one vial containing sufficient toxin for ten tests; in packages of one vial containing sufficient toxin for 100 tests.

SILVER PREPARATIONS

Silver compounds are used in medicine to secure caustic, astringent, germicidal and antiseptic effects. These results are produced by the free silver ions. When caustic effects are desired, silver nitrate is preferred, because the organic compounds of silver are largely or completely lacking in caustic properties. As an astringent, also, silver nitrate is the compound of choice; but it must be used in weaker solutions. The antiseptic action of silver nitrate is complicated by irritation, pain, astringency and corrosion. These may be desirable for the destruction of tissue or the stimulation of indolent wounds; but when they are not necessary for such purposes, they are distinctly undesirable. They may be avoided by the use of colloidal silver preparations.

Colloidal Silver Preparations

In these, the silver does not exist to any great extent, as free ions; therefore, it does not precipitate chlorides or proteins, and is noncorrosive, and, relatively or quite, nonastringent and nonirritant. Nevertheless, a considerable degree of antiseptic action is retained. This is not proportional to the total silver content, and varies for the different compounds; suggesting that the antiseptic action is due to the liberation of very low concentrations of silver ions, which vary for the different compounds.

The mechanism of these effects is analogous to the late action of silver nitrate. This takes place in two stages: (1) the immediate irritant and germicidal effects produced by the direct application of the free silver ions; and (2) the later, milder antiseptic effects produced by the re-solution of the silver-protein compounds that were formed in the first stage. If the second stage alone is desired (i. e., mild antisepsis without irritation), the direct application of the colloid compounds may have advantages over their indirect production from silver nitrate, aside from the avoidance of irritation. The absence of any coagulation membrane facilitates their access to the cells; they form more concentrated solutions than are likely to be formed from the re-solution of the silver precipitates *in situ;* the colloidal aggregates may be smaller and therefore more reactive; and because of the absence of irritation, they are likely to be more frequently applied and would for that reason secure a more continuous action.

The colloidal silver preparations appear to be quite efficacious for the prophylaxis against gonorrheal infection, evidently killing these organisms on direct contact. Culver (*J. Lab. & Clin. Med.* **3**:487 [May] 1918) reports that gonococci in hydrocele broth cultures are killed by momentary exposure to from 0.5 per cent mild silver-protein or to 0.25 per cent strong silver-protein. As regards other organisms, discordant results have been reported:

Metallic silver and insoluble compounds of silver, such as the oxide, the halogen salts (iodide, chloride, etc.) and silver protein precipitates, may be brought into "colloidal solution"; i. e., if they are sufficiently finely divided, they become miscible with water, so that they apparently go into solution (although such "colloidal solutions" are strictly permanent "suspensions" of the insoluble substance in a state of ultramicroscopic particles).

The commercial preparations are for the most part produced by dissolving reduced silver or silver oxide, or some protein-silver precipitate, in an excess of a denatured protein, and drying *in vacuo.* This results in substances that dissolve very freely, although somewhat slowly, in water, yielding brown "colloid solutions" which contain so little of free silver ions that they do not readily precipitate chlorides or proteins. They consist of probably indefinite mixtures of metallic silver, silver oxide, and various silver-protein compounds, all in colloidal form. The proportions of these and the properties of the mixture vary according to the conditions under which they are produced. Although there are probably all kinds of gradations, most of the products on the market fall into a small number of fairly definite therapeutic groups:

(A) Strong Silver-Protein Type.

(B) Mild Silver-Protein Type.

(C) Collargol Type.

(D) Electric Type.

A. Strong Silver-Protein Type.—Strong silver-protein compounds contain the lowest percentage of silver (from 7.5 to 8.5 per cent), but have the strongest germicidal action, and are distinctly irritant. They are, therefore, therapeutically intermediate between silver nitrate and mild silver-protein. The following products listed in N. N. R. belong to this group: proganol; protargentum-Squibb, and protargol.

Protargol is said to be prepared by precipitating a "peptone" (albumose) solution with silver nitrate, or with moist silver oxide; dissolving the silver peptonate in an excess of protalbumose; and drying *in vacuo* (Fraenkel).

	Strong Silver-Protein Per Cent	Mild Silver-Protein Per Cent
Eye:		
Conjunctivitis, simple, purulent or gonorrheal	2 to 10	Solution, 25 Ointment, 10
Prophylaxis against ophthalmia neonatorum	2 to 10	25
Prophylaxis before ophthalmic operations (several days)		25
Corneal ulcers		50
Nose and throat	0.5 to 10	Spray, 10 to 20 Swab, 25 to 50
Wounds and ulcers		1 to 10, solution or ointment 10, dusting powder
Gonorrhea:		
Injections—Prophylactic	2	10
Acute	¼ to 1	3 to 10
Chronic	2 to 10	10 to 20
Urethral irrigation	1: 2,000 to 1: 1,000	1: 1,000
Urethral suppositories	5 to 10	20 (0.13 Gm. or 2 grains)
Cystitis		20 to 50 (5 cc.) or 10 to 25 (30 cc. left in the bladder)
Gynecologic practice:		
Solutions	2 to 10	25 (tampons of solution in glycerin)
Tampons	5	
Ointments	2	
Suppositories	5	Suppositories, 20 (0.3 Gm. or 5 grains)
Rectal:		
Irrigation	0.1	0.1 to 1
Injection	2	10
Suppositories	5 to 10	20 (0.13 Gm. or 2 grains)
Oral administration	0.002 to 0.015 Gm. (1/32 to ¼ grain)	0.3 Gm. (5 grains)
Pyelography		2 (solargentum) 50 (cargentos)

Protargentum-Squibb is said to be prepared by a quite different process; i. e., by the action of silver nitrate on gelatin, in the presence of an alkali, precipitation by alcohol, and drying.

B. Mild Silver-Protein Type.—Mild silver-protein compounds contain from 19 to 25 per cent of silver, but are quite nonirritant. The following products listed in N. N. R. belong to this group: argyn; cargentos; silvol; solargentum-Squibb.

Argyn is defined as a colloidal compound of silver oxide and serum albumin.

Solargentum-Squibb is prepared from alkali-gelatin, used as a solvent for silver oxide. The solution is then concentrated and dried *in vacuo*.

Cargentos is prepared by suspending moist silver oxide in a solution of casein, and heating the mixture until no precipitate is obtained on the addition of solution of sodium chloride, and by evaporating the mixture to dryness in an air oven.

C. Collargol Type. — This contains a much higher percentage (78) of silver, said to be in the form of metallic silver, reduced to the colloidal form by chemical means, and "stabilized" by "a small percentage of egg albumin with products of oxidation." However, the albumin is denatured, since it does not precipitate on boiling; and it presumably constitutes the greater part of the 22 per cent that is not silver. Collargol, therefore, differs from the preceding class in degree rather than in principle, containing a larger proportion of silver in the form of colloidal-metal and oxide, and a smaller proportion in the form of proteinate. Its therapeutic field has been mainly for intravenous and intramuscular injection. According to the results of Bottner (*München. med. Wchnschr.* **68**:876 [July 15] 1921) the therapeutic response would appear to be due to the foreign proteins, rather than to the silver.

D. Electric Type. — Metallic silver may be brought into colloidal solution electrically, i. e., by forming an arc between silver electrodes under water. These solutions are, however, very dilute, and are not sufficiently stable for concentration. They are also likely to contain silver oxide, and sometimes ionized silver.

Therapeutic Uses. — The colloidal silver compounds are used mainly on mucous membranes, for antisepsis. The strong silver-protein group is most effective in this respect, but is slightly irritant and stimulant. The mild silver-protein group acts also largely as mucilaginous demulcent and protective; and as detergent, by dislodging pus. Collargol acts locally like the mild silver-protein group, but is used mainly to produce systemic reactions.

The antiseptic efficiency of the silver compounds and their content of silver ions may be conveniently compared by their restraining effect on gas-formation by yeast, according to the method of Dreser, as modified by Pilcher and Sollmann (*J. Lab. & Clin. Med.*, **8**:301, 1923). According to this, the following solutions approximately equal the efficiency of a 1 in 1,000 solution of silver nitrate in the same media (*J. Lab. & Clin. Med.* **9**:260, 1924): protargol in water 1 per cent, in physiological solution of sodium chloride 0.125 per cent, in blood 0.9 per cent; and silvol in water 36 per cent, in physiological solution of sodium chloride 1 per cent, in blood 3 per cent.

The silver-proteins have been administered by mouth as gastro-intestinal antiseptics. It appears most improbable that the low concentration that could be secured in this manner would have any antibacterial action; there is no decisive clinical evidence of such an effect.

Dosage and Administration.—The concentrations for mucous membranes range from 0.1 to 10 per cent for strong silver-protein; from 5 to 50 per cent for mild silver-protein, and from 0.02 to 1 per cent for collargol. These are applied every two to four hours, if possible. Solutions should be recently prepared, and should be protected against light. Ointments and suppositories are used with the same concentrations as the aqueous solutions. Stains on linen are removed by 1 in 1,000 solution of mercuric chloride. The usual concentrations for special purposes are shown in the adjoined table.

(Early Preventive) Treatment of Venereal Diseases.—The ordinary routine consists in washing the parts thoroughly with soap and water, after which the urethra is injected with a 2 per cent strong silver-protein solution, which is held in the urethra for five minutes. The glans is then inuncted with 30 per cent calomel ointment for five minutes.

The efficacy is marked if the treatment is applied thoroughly within an hour after exposure, and is fair up to three hours. In the A. E. F., the ratio of diseases to exposure was about 1 in 30 without prophylactic treatment, and 1 in 90 with treatment. Prophylaxis, therefore, reduced the incidence to about one third (Ashburn, 1919). It is practically useless after five hours.

STRONG SILVER-PROTEIN.—Argento-Proteinum Forte. Protargin Strong.—For description see the U. S. Pharmacopeia under Argento-Proteinum Forte.

Actions, Uses and Dosage.—See preceding article, Silver Preparations. Solutions are best prepared by dusting the powder on the surface of cold water, and allowing it to dissolve without stirring or shaking. This requires about ten minutes. Solutions should be freshly prepared.

Protargentum-Squibb.—A brand of strong silver-protein-U. S. P. Protargentum is a compound of gelatin and silver.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

Tablets Protargentum-Squibb, 4.6 grains.

Protargol.—A brand of strong silver-protein-U. S. P. Protargol is a compound of albumin and silver.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent expired. U. S. trademark 30,882.

MILD SILVER-PROTEIN.—Argento-Proteinum Mite.—Protargin Mild.—For description see the U. S. Pharmacopeia under Argento-Proteinum Mite.

Actions, Uses and Dosage. — See preceding article, Silver Preparations.

Argyn.—A brand of mild silver-protein-U. S. P. Argyn is a colloidal compound of silver oxide and serum albumin.

Manufactured by The Abbott Laboratories, North Chicago. No U. S. patent. U. S. trademark 137,522.

Argyn Tablets, 6 grains.

Cargentos.—Argenti Oxidum Colloidale-Mulford.—A brand of mild silver-protein-U. S. P. Cargentos is a colloidal preparation of silver oxide and modified casein.

Manufactured by the H. K. Mulford Company, Philadelphia. U. S. patent 1,043,646 (Nov. 5, 1912; expires 1929). No U. S. trademark.

Cargentos Capsules, 3 Grains.—Capsules of Colloidal Silver Oxide-Mulford, 3 grains.

Cargentos Ointment, 5 Per Cent.—Ointment of Colloidal Silver Oxide-Mulford, 5 per cent: Cargentos, 1 part; anhydrous wool fat, 19 parts; put up in collapsible tubes.

Cargentos Ointment, 10 Per Cent.—Ointment of Colloidal Silver Oxide-Mulford, 10 per cent: Cargentos, 1 part; anhydrous wool fat, 9 parts, put up in collapsible tubes.

Cargentos Urethral Suppositories.—Colloidal Silver Oxide Urethral Suppositories or Bougies-Mulford: Each suppository weighs about 2.5 Gm. (37 grains). The vehicle consists of glycerite of boroglycerin, gelatin and water.

Silvol.—A brand of mild silver-protein-U. S. P. Silvol is a compound of colloidal silver with an alkaline proteid.

Manufactured by Parke, Davis and Company, Detroit. No U. S. patent or trademark.

Silvol Bougies 5 Per Cent: Bougies weighing 0.81 Gm. (12.5 grains) and containing silvol 5 per cent in a base composed of oil of theobroma, wool fat, white wax, acacia and glucose.

Silvol Ointment 5 Per Cent: Silvol, 5 per cent in a base composed of petrolatum, wool fat, benzoinated lard and white wax.

Vaginal Suppositories Silvol 5 Per Cent: Suppositories weighing 8.45 Gm. (130 grains) and containing silvol, 5 per cent, in a base composed of gelatin and glycerin.

Solargentum-Squibb. — A brand of mild silver-protein-U. S. P. Solargentum-Squibb is a compound of silver and gelatin, containing from 19 to 23 per cent of silver in colloidal form.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

Tablets Solargentum-Squibb, 4.6 grains.

COLLARGOL.—Collargolum.—Colloidal Silver.—Argentum Colloidale. — Argentum Credé. — Colloidal silver and silver oxide, formed by reduction and stabilized by derived egg-albumin, with which it is possibly partly combined. Collargol contains silver equivalent to approximately 78 per cent metallic silver, of which about 2 per cent is ionized. It forms, with water, a fairly stable colloidal suspension.

Actions and Uses.—The intravenous injection of collargol is followed, after from two to four hours, by a chill, fever and leukocytosis. This reaction has been used, with variable results, against general and localized infections, similar to nonspecific protein therapy. Indeed, it is possible that the protein stabilizer may play the principal or sole part in the reaction. The direct antiseptic action is rather feeble, and probably due to contamination with free silver ions.

Dosage.—It is employed in carefully filtered solutions (colloidal suspensions) varying in strength according to the intended use; from 10 to 20 cc. of a 2 per cent solution for intravenous injections (the possible reaction of certain persons to egg protein should be considered); and from 0.02 to 1 per cent solution for washes. Collargol solution should not be sterilized by boiling, but sterile solution mediums should be used. Locally, it is used in the form of a 15 per cent ointment (see collargol ointment), from 2 to 4 Gm. (30 to 60 grains) being very thoroughly rubbed into the skin; in the form of 5 per cent dusting powder, prepared with finest clay; of bougies containing 0.2 Gm. (3 grains), and vaginal suppositories and tampons each containing 0.05 Gm. (¾ grain); for parenchymatous injections in from 0.5 to 1 per cent glycerin solutions. Internally, it may be administered as tablets containing 0.06 Gm. (1 grain), or, as a solution (colloidal suspension) of from 1 in 500 to 1 in 100, may be added to the food in teaspoonful doses.

Manufactured by the Heyden Chemical Company of America, Inc., Garfield, N. J. (Schering and Glatz, Inc., Bloomfield, N. J., and New York, N. Y.). U. S. trademark 32,452.

Collargol Ointment.—Unguentum Credé.—Ointment of Colloidal Silver.—Collargol ointment is an ointment containing 15 per cent of collargol.

Collargol occurs as small, hard, brittle, bluish-black scale-like pieces. With 20 parts of distilled water, it forms a colloidal suspension, black in incident light, and reddish brown in transmitted light, which remains stable for months. The addition of albumin to collargol prevents or delays its precipitation by acids and salts. A sufficient amount of albumin to prevent its precipitation under ordinary conditions is, therefore, added to collargol during its manufacture. Hense, collargol, when added to spring or well-water containing salts, undergoes no change, whereas, colloidal silver containing no albumin precipitates on being boiled. Collargol solutions brought once to the boiling point present no macroscopic changes, though they do decrease in stability.

A colloidal suspension of collargol does not respond directly to the usual tests for silver. If the colloidal suspension is warmed with nitric acid a white cloudiness is produced, which clears completely on standing, and the silver can then be demonstrated in the usual manner. If a fragment of collargol is heated on a platinum scoop, shining white metallic silver of the ordinary kind, insoluble in water, is at once formed.

Its colloidal suspension should not be exposed to light, or air; it is incompatible with the usual silver reagents.

Collargol ointment is prepared by incorporating 15 parts of collargol with 5 parts of water, 10 parts of white wax and 70 parts of benzoinated lard, taking care that the soluble silver shall not be transformed into metallic silver of the ordinary kind. This, it is asserted, is liable to occur unless great care is observed in the manipulation.

The natural color of collargol ointment is reddish brown. The ointment is good as long as it colors the skin black.

LUNOSOL.—Argenti Chloridum Colloidale Saccharatum-Hille.—A preparation of colloidal silver chloride containing silver chloride, 10 per cent, and sucrose, 90 per cent.

Actions and Uses.—Lunosol has antiseptic and germicidal properties. It causes neither irritation of the mucous membranes nor coagulation of albumin even in concentrated solutions; it does not stain the skin.

Lunosol is intended for the prophylaxis against and treatment of infections of the accessible mucous membranes, such as the genito-urinary tract and the eye, ear, nose and throat.

Dosage.—Lunosol is generally used in solutions (colloidal suspensions) of from 1 to 25 per cent. In the male urethra, from 3 to 25 per cent solutions are used; for irrigation of the vagina, a 1 per cent solution is used, and on tampons, a 10 per cent solution; for irrigation of the bladder, a 0.1 to 1 per cent solution, and for irrigation of the rectum, a 1 to 5 per cent solution is used; in ophthalmia neonatorum, 25 to 50 per cent solutions are applied; in pyelitis, 3 to 10 per cent solutions are injected into the kidney pelvis; for application to the nose, eye and ear, the average concentration is 10 per cent.

Manufactured by Hille Laboratories, Inc., Chicago. No U. S. patent. U. S. trademark 189,347.

Lunosol Capsules, 6 grains.

Lunosol is a white, slightly hygroscopic, granular powder, odorless, having a sweetish, metallic taste. It is completely soluble in one half of its weight of water, forming an opalescent solution (colloidal suspension) which is bluish white in reflected light and reddish in transmitted light.

If a solution of 0.5 Gm. of lunosol in 25 cc. of water is treated with 0.6 Gm. of potassium iodide dissolved in a few cc. of water, a yellow liquid is formed. If 5 Gm. of lunosol is dissolved in 25 cc. of water and 8 cc. of strong ammonia water is added, a clear, colorless solution results. If a solution of 0.5 Gm. of lunosol in 10 cc. of water is treated with 15 cc. of tenth-normal sodium thiosulphate, a clear colorless solution results. Place a few drops of lunosol solution (1 in 10) in the nostril: no sensation of irritation is produced. To about 2 cc. of fresh undiluted egg white, add 1 cc. of lunosol solution (1 in 10); shake the mixture, then allow to stand for fifteen minutes and finally dilute with 15 cc. of water: no precipitate forms.

Dissolve approximately 0.5 Gm. of lunosol, accurately weighed, in 25 cc. of water, add 8 cc. of stronger ammonia water followed by an excess of nitric acid. Collect, wash, dry and weigh the precipitate. The weight of silver chloride found corresponds to a content of 10 per cent of silver chloride in the specimen taken.

NEO-SILVOL. — Colloidal silver iodide compound. — A compound of silver iodide with a soluble gelatin base containing 18 to 22 per cent of silver iodide in colloidal form.

Actions and Uses.—Neo-Silvol, even in concentrated solutions, causes neither irritation of mucous membranes nor coagulation of albumin. It does not stain the skin.

It is claimed that neo-silvol in laboratory tests for germicidal value has been found as effective as phenol in its action on bacteria.

Neo-silvol is intended for the prophylaxis against, and treatment of infections of accessible mucous membranes and is claimed to be indicated in infections of the genito-urinary tract and of the eye, ear, nose and throat.

Dosage.—In the treatment of acute inflammations of the mucous membranes solutions of neo-silvol as strong as 50 per cent may be used. In inflammatory infections of the ear, nose and throat, 5 to 40 per cent solutions are used; for irrigating sinuses 2 to 5 per cent; for inflammatory conditions of the eye and conjunctival infections in strength of 10 to 40 per cent; in acute anterior urethritis, as an abortive measure, 20 per cent; for posterior urethritis or in the routine treatment of anterior urethritis, 10 per cent; in the genito-urinary tract of the female, from 10 to 50 per cent.

Solutions of neo-silvol are prepared by adding the substance to the required amount of water and agitating the mixture until solution occurs.

Manufactured by Parke, Davis and Co., Detroit, Mich. U. S. patent and trademark applied for.

Capsules Neo-silvol, 6 grains.

Neo-Silvol Ointment 5 Per Cent.: Neo-Silvol, 5 per cent., in a base composed of glycerin and benzoinated lard, hydrous wool fat and petrolatum.

Neo-Silvol Vaginal Suppositories: Each suppository contains neo-silvol, 0.4536 Gm. (7 grains), in a base composed of gelatin, glycerin and water.

Neo-silvol is prepared by heating freshly precipitated silver oxide with gelatin (which has been previously dissolved in a dilute alkaline solution) until the silver oxide has been reduced to metallic silver in a colloidal state of subdivision. The solution is treated with iodine, which combines with the silver. The liquid is then evaporated to dryness *in vacuo*. The finished product contains from 1 to 3 per cent of combined iodine in excess of that required for combination with the silver.

Neo-silvol occurs as pale yellow granules. In concentration up to 50 per cent neo-silvol forms with water almost colorless, milky or opalescent solutions (*colloidal suspensions*). Neo-silvol is insoluble in fixed oils, but slowly soluble in glycerin. Solutions of neo-silvol are not precipitated in the cold by strong acids or sodium chloride.

If a solution of neo-silvol is treated with a solution of potassium hydroxide no precipitate of silver iodide is formed; if this solution is boiled for a few minutes, it darkens gradually, but no precipitate is formed unless it is allowed to stand for some time. If a solution of neo-silvol is treated with dilute hydrochloric acid silver iodide is not precipitated; if this mixture is now boiled, the silver iodide is gradually precipitated. Dilute solutions of neo-silvol do not discolor in sunlight (*absence of silver chloride and silver bromide*).

Transfer about 1 Gm. of neo-silvol, accurately weighed, to an 8 ounce Erlenmeyer flask containing 100 cc. water and heat on steam bath until "solution" is effected. Add 5 cc. of hydrochloric acid and boil gently over a flame for ten or fifteen minutes; cool; when sufficiently cool to handle, filter through a tared Gooch crucible containing a fairly thick pad of asbestos. Wash thoroughly with water acidulated with hydrochloric acid (0.3 per cent hydrochloric acid). Dry at 100 C. and weight as silver iodide: the weight found is equivalent to 18 to 22 per cent of silver iodide.

Simple Silver Salts

SILVER CITRATE.—Argenti Citras.—$Ag_3C_6H_5O_7$.—The normal silver salt of citric acid.

Actions and Uses.—Silver citrate is a nonirritating antiseptic.

It is said to be useful in the treatment of wounds, ulcers, gonorrhea, and other diseases of the mucous membranes.

Dosage.—It may be applied in substance to wounds. Solutions of from 1 in 4,000 to 1 in 10,000 are recommended for injection into the body cavities, the urethra, etc.

Solution of citric acid is neutralized with sodium carbonate and a solution of silver nitrate added, with constant stirring. The precipitate is allowed to subside, washed with water, and dried on porous plates. The entire operation must be conducted under protection from the light.

Silver citrate forms an odorless, heavy powder, which is moderately sensitive to the light. It is almost insoluble in water. Pure silver citrate, when heated to redness, leaves a residue of metallic silver weighing 63.16 per cent of the weight of the original salt.

It should be carefully protected from the light.

Silver Citrate-Merck.—A brand of silver citrate-N. N. R. On heating it yields not less than 62 per cent of metallic silver.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

SILVER LACTATE. — Argenti Lactas.—$Ag.C_3H_5O_3+H_2O$. —The normal silver salt of lactic acid.

Actions and Uses.—Silver lactate is used as an active antiseptic. The 1 in 300 to 1 in 500 aqueous solution is said to be equal in disinfecting power to a 1 in 1,000 solution of mercuric chloride. It is irritating if applied in substance to wounds.

Dosage.—From 1 in 100 to 1 in 2,000 solutions.

Silver lactate is prepared by dissolving freshly precipitated silver carbonate in a solution of lactic acid by the aid of heat, and concentrating the solution until crystallization begins. The operation must be conducted in a darkened room.

Silver lactate occurs in the form of crystalline needles, granular masses or crystalline powder; it dissolves in about 15 parts of water. Pure silver lactate when heated leaves a residue of metallic silver, weighing 50.2 per cent. It is usually colored somewhat brown and gives with water a brownish or reddish solution. The salt must be protected from the light.

Silver Lactate-Merck.—A brand of silver lactate-N. N. R. On heating it yields from 50 to 51.5 per cent of metallic silver.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

SILVER NITRATE.—For description see the U. S. Pharmacopeia and Useful Drugs under Argenti Nitras.

Ampoule Solution Silver Nitrate 1 Per Cent-Cutter: Solution silver nitrate 1 per cent, approximately 0.2 cc., contained in ampules composed of beeswax.

Dosage.—For the prevention of ophthalmia neonatorum, two drops are placed in each eye after preliminary cleansing.

Prepared by the Cutter Laboratory, Berkeley, Calif. No U. S. patent or trademark.

Ampule Solution Silver Nitrate 1 Per Cent-Lederle: solution silver nitrate 1 per cent approximately 0.2 cc. contained in ampules composed of beeswax.

Dosage.—A pinhole is made at one end of the ampule, and, after suitable preliminary cleansing of the eye, two drops are placed in each eye of the newborn.

Prepared by Lederle Antitoxin Laboratories, New York. No U. S. patent or trademark.

Capsules Solution Silver Nitrate, 1 Per Cent-P. D. & Co., 6 minims: The aqueous solution of silver nitrate is contained in capsules composed of beeswax with an inner lining of paraffin.

Dosage.—For use in prophylaxis against ophthalmia neonatorum, a pinhole is made in one end of the capsule and three drops of the solution placed in the eye of the newborn.

Prepared by Parke, Davis & Co., Detroit. U. S. patent applied for. No U. S. trademark.

Causticks, Caustick Applicators and Special Caustick Applicators.—(Silver Nitrate 75 per cent): Wooden sticks 1½, 5½ and 12 inches (3.8, 14.0, 16.4 and 30.4 cm.) long, respectively, tipped with a mixture of silver nitrate 75 per cent, and potassium nitrate 25 per cent. Each stick is to be used but once.

Prepared by Tappan Zee Surgical Co., Nyack, N. Y. No U. S. patent or trademark.

SODIUM PHOSPHATE.—For description see the U. S. Pharmacopeia or Useful Drugs under Sodii Phosphas.

Sofos: A mixture of sodium dihydrogen phosphate and sodium hydrogen carbonate (sodium bicarbonate), rendered stable by coating the particles of one of the constituents with disodium hydrogen phosphate. One part of sofos has the same phosphate value as 1.75 parts of sodium phosphate, U. S. P. When sofos is treated with water, sodium phosphate (Na_2HPO_4) is formed and carbon dioxide is set free. (The reaction does not go to completion, some sodium dihydrogen phosphate remaining; but this is not considered important, as primary phosphate is also formed when sodium phosphate is taken into the acid gastric fluid.) Sofos differs from the effervescent sodium phosphate preparations in that it is free from citrate or tartrate.

Manufactured by the General Chemical Company, New York. U. S. patent 1,037,078 (Aug. 27, 1912; expires 1929) and 1,150,901 (Aug. 4, 1915; expires 1932). U. S. trademark 116,426.

SOLUTION OF INVERT SUGAR-LILLY.—A solution of a mixture of dextrose and levulose obtained by the inversion of sucrose.

Actions and Uses.—Solution of invert sugar-Lilly is used in the injection treatment of varicose veins. It is claimed that the use of sugar solutions such as solutions of dextrose or of invert sugar have the advantage over solutions of sodium chloride, sodium salicylate or mercuric chloride in that they do not cause severe cramps or sloughing if accidentally injected outside the vein.

Dosage.—Depending on the size of the vein, from 5 to 20 cc. of solution is injected. For young patients whose veins react to solutions of less concentration, solutions containing from 50 to 60 Gm. of invert sugar in 100 cc. are used; for older patients and varicosities of long standing, a solution containing 75 Gm. of invert sugar in 100 cc. is used.

Manufactured by Eli Lilly & Co., Indianapolis. No U. S. patent or trademark.

Solution of Invert Sugar-Lilly, 5 Gm. in 10 cc.

Solution of Invert Sugar-Lilly, 6 Gm. in 10 cc.

Solution of Invert Sugar-Lilly, 7.5 Gm. in 10 cc.

Solution of invert sugar-Lilly is prepared by inverting cane sugar with tartaric acid and adjusting to a *p*H of 6.8 with sodium hydroxide.

Solution of Invert sugar-Lilly is a clear, pale amber, sweet, watery solution.

A 10 cc. portion requires less than 2 cc. of tenth-normal sodium hydroxide to neutralize the acid, phenolphthalein being used as an indicator. No sediment separates from the solution in ampules on prolonged standing (*insoluble salts, ultramarine or prussian blue*). A 10 per cent solution is not affected by the addition of an equal volume of hydrogen sulphide solution (*heavy metals*). Ten cc. portions of a 10 per cent solution remain clear for at least one minute after the addition of 1 cc. of silver nitrate solution (*chloride*) or of ammonium oxalate solution (*calcium*). A portion equivalent to 5 Gm. of invert sugar shows no more sulphate than corresponds to 0.3 cc. of fiftieth-normal sulphuric acid according to the U. S. P. X test. A solution equivalent to 5 Gm. of invert sugar evaporated to dryness and ashed yields a residue weighing not more than 0.004 Gm. A solution equivalent to 5 Gm. of invert sugar yields not more ammonia than is equivalent to 0.5 cc. of hundredth-normal hydrochloric acid. A solution containing 16 per cent of invert sugar calculated from its copper reducing power when examined by means of the polariscope has a specific rotation of $\alpha \frac{25}{\mathrm{D}}$ between — 16 and — 18.5.

Dilute exactly 10 cc. of the original to exactly 500 cc.; transfer 10 cc. of this solution to a 250 cc. beaker and assay for invert sugar according to paragraphs 35 and 36 on pages 190 and 191 of the 1925 edition of the A. O. A. C. Manual: the amount of invert sugar is within 5 per cent of the amount claimed. Transfer 50 cc. of the prepared solution to a 100 cc. standard flask; invert according to paragraph 23-C, page 187 of the A. O. A. C. Manual and assay for sucrose according to paragraph 28, page 189 of the A. O. A. C. Manual: the weight of sucrose is not greater than 4 per cent of the weight of invert sugar found.

SULPHOICHTHYOLATE PREPARATIONS AND SUBSTITUTES

Preparations containing as their essential constituents salts or compounds of a mixture of acids containing sulphur and designated by the group name "sulphoichthyolic acid" are obtained from certain bituminous shales. Sulphoichthyolic acid is characterized by a high sulphur content, the sulphur existing largely in the form of sulphonates, sulphones and sulphides. The ammonium compound of this so-called sulphoichthyolic acid—first introduced as ichthyol—has been used most extensively. Compounds with sodium and other metals, with albumin, with formaldehyde, etc., have also been introduced.

A number of more or less related compounds of sulphur have been introduced as substitutes for the sulphoichthyolates; and the National Formulary contains a sulphoichthyolate preparation under the title, "Sulphonated Bitumen."

Actions and Uses.—The current estimate of the effects of sulphoichthyolic acid preparations is based largely on the use of ichthyol. The use of sulphoichthyolate preparations is still largely empiric. They are weakly antiseptic and emollient. Taken internally, they produce some gastro-intestinal irritation, with diarrhea, etc.

They were formerly used locally under the supposition that they secure the absorption of swellings and effusions in contusions, burns, etc., and especially in gynecologic practice, and in various skin diseases. They have been tried internally in a great variety of conditions, but there is no evidence that they are of any therapeutic value when used in this way.

HIRATHIOL.—Ammonii Sulphoichthyolicum.—An aqueous solution of a synthetic product, the important medicinal constituents of which are ammonium compounds containing sulphur in the form of sulphonates, sulphones and sulphides. It complies with the standards for Sulphonated Bitumen, N. F.

Actions and Uses.—See preceding article, Sulphoichthyolate Preparations and Substitutes.

Manufactured by Hirasawa Chemical Industrial Company, Tokyo, Japan (Takamine Laboratory, Inc., Clifton, N. J., U. S. selling agent). No U. S. patent. U. S. trademark 117,964.

Hirathiol is a brownish-black syrupy liquid, having a characteristic empyreumatic odor. It is soluble in water, glycerin and alcohol. It is miscible with fats.

The aqueous solution of hirathiol (1 in 10) is faintly acid to blue litmus. The aqueous solution (1 in 20) yields a greenish-black, resin-like precipitate on the addition of hydrochloric acid. This precipitate is soluble in ether; it is also soluble in water, but if dissolved in the latter solvent, it is again precipitated by the addition of hydrochloric acid or sodium chloride solution.

Boil an aqueous solution of hirathiol (1 in 10) with potassium hydroxide solution: ammonia is evolved. Hirathiol is decomposed by acids, saline solutions, and fixed alkalis.

Hirathiol loses 46.5 per cent of its weight when dried at 100 C.

Weigh from 5 to 6 Gm. of hirathiol into a flask, and 25 cc. of potassium hydroxide solution and 100 cc. of water. Distil the mixture until no more ammonia passes over, collect the distillate in 15 cc. of normal sulphuric acid, to which 1 drop of methyl orange solution has been added, and titrate the excess of acid with tenth-normal potassium hydroxide: the amount of normal sulphuric acid consumed corresponds to 3.18 per cent of total ammonia (NH_3).

Weigh from 5 to 6 Gm. of hirathiol into a beaker, add 50 cc. of water and 10 cc. of a 10 per cent solution of albumin, followed by 5 portions of 5 cc. each of diluted hydrochloric acid, shaking after each addition. Make up the mixture to a volume of 500 cc. and filter through a dry filter. Heat 200 cc. of the filtrate to boiling, add 10 cc. of barium chloride solution and allow the mixture to stand for twenty-four hours. Collect the precipitate of barium sulphate, heat and weigh: The weight of barium sulphate obtained corresponds to 6.16 per cent of ammonium sulphate.

Weigh from 0.5 to 1 Gm. of hirathiol into a Kjeldahl flask, add 30 cc. of water and 5 Gm. of potassium chlorate followed by 30 cc. of nitric acid, and evaporate the mixture to about 5 cc.; add 25 cc. of hydrochloric acid and evaporate to 5 cc.; again add 25 cc. of hydrochloric acid and evaporate to 5 cc. Then add 100 cc. of water, heat to boiling and add 10 cc. of barium chloride solution, allow the mixture to stand for twenty-four hours, collect the precipitate of barium sulphate, heat and weigh: the weight of barium sulphate corresponds to 10.23 per cent of total sulphur.

Calculate the ammonia obtained in the ammonium sulphate, as previously determined in hirathiol, and subtract the result from "total ammonia" as previously determined. Multiply the remainder by the factor 1.88: the result represents the sulphur present as "sulphonic sulphur." Calculate the sulphur contained in the ammonium sulphate as previously determined in hirathiol, and subtract the result from "total sulphur" as previously determined: the remainder (8.74 per cent) represents the sulphur present in the organic, sulphonic acids contained in the substance. Subtract the "sulphonic sulphur" as previously calculated, from the sulphur in the organic acids, as previously calculated: the remainder corresponds to 5.73 per cent of organic ("sulphide") sulphur.

ICHTHYNAT.—**Ammonium Ichthynatum.**—An aqueous solution, the important medicinal constituents of which are ammonium compounds containing sulphur in the form of sulphonates, sulphones, and sulphides. These characteristic forms of sulphur result from the sulphonation of the tarlike distillate obtained from certain bituminous shales. It complies with the standards for Sulphonated Bitumen, N. F.

Actions and Uses.—See preceding article, Sulphoichthyolate Preparations and Substitutes.

Manufactured for the Heyden Chemical Corporation, New York. No U. S. patent. U. S. trademark 44,053.

Ichthynat is a brown-black, syrupy liquid, having a characteristic, empyruematic odor and burning taste.

It is completely soluble in water; incompletely soluble in alcohol or ether, but nearly soluble in a mixture of equal volumes of alcohol and ether; also soluble in a mixture of equal volumes of alcohol, water and ether. It is miscible with glycerin. Ichthynat is decomposed by acid and saline solution, fixed alkalis, their carbonates and iodides, alkaloidal salts and mercuric chloride.

The aqueous solution of ichthynat (1 in 10) has a faintly acid reaction on blue litmus paper. The aqueous solution of ichthynat (1 in 10) yields a greenish-black, resin-like precipitate on the addition of hydrochloric acid. This precipitate is soluble in ether; it is partially soluble in alcohol; soluble in water, but if dissolved in the latter solvent it may again be precipitated from solution by the addition of hydrochloric acid or sodium chloride solution. With barium chloride solution the aqueous solution of ichthynat (1 in 10) gives a brownish-black precipitate which is insoluble in diluted hydrochloric acid. If the aqueous solution of ichthynat (1 in 10) is boiled with potassium hydroxide solution, ammonia is evolved. If 1 Gm. of ichthynat is ignited it will leave not more than 0.5 per cent of residue. If 10 Gm. of ichthynat is diluted with 90 cc. of water, the mixture placed in a glass-stoppered cylinder and allowed to remain undisturbed for twenty-four hours, no deposit will form.

If dried at 100 C., ichthynat will not lose more than 47.0 per cent of its weight (absence of an undue amount of *water*). If from 5 to 6 Gm. of ichthynat is weighed into a flask, and 25 cc. of potassium hydroxide solution and 100 cc. of water is added, the mixture distilled until no more ammonia passes over, the distillate collected in 15 cc. of normal sulphuric acid to which 1 drop of methl orange solution has been added and the excess of acid then titrated with tenth-normal potassium hydroxide, the amount of normal sulphuric acid consumed will correspond to from 3 to 5 per cent of total ammonia (NH_3). If from 5 to 6 Gm. of ichthynat is weighed into a beaker, diluted with 50 cc. of water, 10 cc. of a 10 per cent solution of dried egg albumin added, followed by five portions of 5 cc. each of diluted hydrochloric acid, shaking after each addition, the mixture made up to a volume of 500 cc. and filtered through a dry filter, and if 200 cc. of the filtrate is heated to boiling, and 10 cc. of barium chloride solution is added, the mixture allowed to stand for twenty-four hours, the precipitate of barium sulphate collected, heated and weighed in the usual way, the weight of barium sulphate obtained will correspond to from 5 to 7 per cent of ammonium sulphate. If from 0.5 to 1 Gm. of ichthynat is weighed into a Kjeldahl flask, diluted with 30 cc. of water, and 5 Gm. of potassium chlorate added, followed by 30 cc. of nitric acid the mixture evaporated to about 5 cc., and 25 cc. of hydrochloric acid added, this solution evaporated to about 5 cc., 25 cc. of hydrochloric acid again added, this solution evaporated to about 5 cc., 100 cc. of water added, this solution heated to boiling, 10 cc. of barium chloride solution added, the mixture allowed to stand for twenty-four hours, the precipitate of barium sulphate collected, heated and weighed in the usual way, the weight of barium sulphate will correspond to from 8 to 10 per cent of total sulphur. If the ammonia contained in the ammonium sulphate as previously determined in ichthynat is calculated, and the result subtracted from the "total ammonia" as previously determined, the remainder will represent the ammonia combined with the organic-sulphonic acids. If this value is multiplied by 1.88, the result (from 3 to 5 per cent) will represent the sulphur present in the sulphonic acids in an oxidized state, i. e., the "sulphonic sulphur." If the sulphur contained in the ammonium sulphate as previously determined in ichthynat is calculated, and the result subtracted from the "total sulphur" as previously determined, the remained will represent the sulphur present in the organic sulphonic acids contained in the substance. If the "sulphonic" sulphur in ichthynat as previously calculated is subtracted from the sulphur in the organic-sulphonic acids as previously calculated, the remainder will correspond to at least 5 per cent of "organic" ("sulphid") sulphur.

ISAROL-CIBA.—Sulphonated Bitumen, N. F.—A preparation obtained by dry distillation of bituminous shale. The distillate is sulphonated with sulphuric acid and subsequently neutralized with ammonium carbonate. The product complies with the standards for sulphonated bitumen, N. F.

Actions and Uses: See Sulphoichthyolate Preparations and Substitutes, New and Nonofficial Remedies, 1929, p. 398.

Manufactured by the Society of Chemical Industry in Basle, Switzerland (Ciba Company, Inc., New York). No U. S. patent. U. S. trademark, 97,007.

Isarol-Ciba is a reddish brown to brownish black syrupy liquid with a strong characteristic empyreumatic odor. It is soluble in water and in glycerin, and is miscible with fixed oils and fats. It is partly soluble in alcohol or ether, and entirely soluble in a mixture of equal volumes of these solvents. An aqueous solution (1 in 10) may be faintly acid or faintly alkaline to litmus paper. The addition of hydrochloric acid to this solution precipitates a dark resinous mass which is soluble in ether.

Incinerate a weighed portion of isarol-Ciba: the ash does not exceed 0.5 per cent. Dry a weighed portion on a water bath to constant weight: the loss is not more than 50 per cent.

Accurately weigh about 5 Gm. of isarol-Ciba, dissolve in 100 cc. of water, transfer to a distillation flask, add an excess of sodium hydroxide solution and distil slowly; collect the distillate (about 50 cc.) in 15 cc. of normal sulphuric acid; when the distillation is completed, titrate the excess of sulphuric acid with tenth-normal sodium hydroxide, using methyl orange as indicator: the amount of ammonia found is not less than 2.5 per cent. Accurately weigh about 1 Gm. of isarol-Ciba; transfer to a 100 cc. beaker and add 25 cc. of alcohol; stir thoroughly, filter, and wash the filter with a mixture of equal parts of ether and alcohol until the washings are clear and colorless; dry the residue on the filter at 100 C., cool, and wash the filter with 200 cc. of warm water slightly acidulated with hydrochloric acid; determine the sulphate in the solution by precipitation with barium chloride solution, and after Dry about 1 Gm. of isarol-Ciba on a watch glass to constant weight at 105 C.; pulverize the dried material and transfer about 0.5 Gm., accurately weighed, to a nickel crucible; add about 9 Gm. of sulphur-free sodium peroxide, and mix thoroughly; place the crucible carefully in a beaker containing cold distilled water, which should reach about halfway to the top; ignite the dry mixture in the crucible by thrusting a red hot iron wire through a hole in the cover of the crucible; after complete combustion has taken place, tip the crucible and allow the fused mass to dissolve in the distilled water; add hydrochloric acid in slight excess, heat to boiling, and determine the sulphate in the solution by precipitation with barium chloride solution, and after washing, drying, igniting and weighing, calculate the results to sulphur: the total sulphur should not be less than 10 per cent.

THIGENOL.—Solution of Sodium Sulpho-Oleate-Roche.—A solution of the sodium salts of synthetic sulpho-oleic acids, containing 2.85 per cent of sulphur.

Actions and Uses.—See preceding article, Sulphoichthyolate Preparations and Substitutes.

Manufactured by F. Hoffmann-La Roche & Co., Basle, Switzerland (The Hoffmann-La Roche Chemical Works, New York, distributor). No U. S. patent. U. S. trademark 80,424.

Precipitated sulhpur is dissolved by boiling in the glyceride of oleic acid; the resulting solution is treated with sulphuric acid, during which process sulphurous acid escapes, and a sulpho-oleic acid is separated out. The separated sulpho-acid is then obtained by pouring into water, and subsequently washing thoroughly. By treatment with solution of sodium hydroxide, there results a solution of sodium sulpho-oleate, which is evaporated *in vacuo* until it has a specific gravity of from 1.05 to 1.06.

Thigenol is a dark brown liquid, having a faint sulphurous odor. It is soluble in one or more parts of water, dilute alcohol, glycerin, chloroform, or oily or fatty bases, with any one of which it mixes freely. When water is the vehicle employed, it should be distilled; hard water will cause a precipitate.

Thigenol is incompatible with mineral acids or acetic acid.

SULPHONMETHANES

Two analogous compounds formed by the substitution of sulphone radicals in methane have been applied in therapeutics. The first, sulphonmethane-U. S. P. (sulphonal) is diethylsulphonedimethylmethane; the second, sulphonemethylmethane-U. S. P. (trional) is diethylsulphonemethylethylmethane. The latter has been generally given the preference.

Sulphonmethane is soluble with difficulty and slowly absorbed and its hypnotic action is but slowly established; sulphonethylmethane is somewhat more soluble than sulphonal and acts more quickly. Both drugs are preferably given in hot liquids; and in the case of sulphonmethane, the hypnotic effect is likely to be postponed for several hours. Sometimes it is not developed until the following day. Sulphonethylmethane is usually effective in an hour or two.

The sulphonmethanes in therapeutic doses produce sleep without noticeable effect on the circulation or respiration. In larger doses, acute poisoning occurs, evidenced by disturbances of the digestive organs, the metabolism and the nervous system. When administered for too long a period, cumulation is likely to occur, producing a condition of chronic poisoning which terminates fatally in a large percentage of cases. In such cases, hematoporphyrin derived from hemoglobin turns the urine pink or red. This should serve as a warning, indicating the immediate withdrawal of the drug.

The symptoms of poisoning consist of persisting confusion, ataxia, constipation, vomiting, albuminuria and nephritis.

Dosage.—The usual dose of either sulphonmethane or sulphonethylmethane is 1.0 Gm. with a maximum of 2 Gm. for the first and 4 Gm. for the second. When these drugs are used frequently, the administration should be suspended once in two or three days to allow of complete elimination, and the urine should be examined frequently for hematoporphyrin.

SULPHONMETHANE.—For description see the U. S. Pharmacopeia and Useful Drugs under Sulphonmethanum.

Actions, Uses and Dosage.—See preceding article, Sulphonmethanes.

Sulphonal.—A nonproprietary name applied to sulphonmethane.

SULPHONETHYLMETHANE.—For description see the U. S. Pharmacopeia and Useful Drugs under Sulphonethylmethanum.

Trional.—A nonproprietary name applied to sulphonethylmethane.

TANNIC ACID DERIVATIVES

The pharmacologic actions of tannic acid are due to its property of precipitating protein. Internally, tannic acid has been used in diarrhea; but if tannic acid is given as such, it is rapidly dissolved in the stomach, and may then produce excessive gastric irritation, nausea and even vomiting. The desire to avoid these effects has prompted the introduction of relatively insoluble compounds of tannin, which would act but little, if at all, in the stomach; and whose action would extend farther down the intestines. This was sought to be accomplished by utilizing the differences in reaction (hydrogen ion concentration) at the various levels of the alimentary tract. It was therefore aimed to make the compounds insoluble in diluted acids, and soluble in diluted alkalis. This object, however, has not been entirely attained and is probably not really desirable in view of the frequent slightly acid reaction of the intestinal contents. It is probably more important that the compounds should be but slowly soluble in any reaction that occurs in the alimentary tract.

Types of Tannic Acid Derivatives.—Four types have been marketed: (1) organic esters of tannic acid, represented by acetyltannic acid (acetyltannic acid-U. S. P., tannigen); (2)

coagulated tannin proteinate, represented by exsiccated tannin albuminate (albumin tannate-U. S. P.); (3) tannin caseinate (protan); and (4) a heterogenous group of other compounds, such as bismuth salts of tannic acid, etc. The chief criteria for evaluating the tannic acid compounds are their solubilities or speed of hydrolysis during various reaction periods in acid and alkaline solution, with or without the addition of ferments.

Importance of Differences in Solubility.—All the compounds are somewhat soluble in water; but not sufficiently soluble to affect their therapeutic usefulness. From the latter standpoint, the solubility in acid gastric juice and the solubility in sodium bicarbonate solution, representing the maximum alkalinity of the intestines, are most important. The speed or slowness of solution is at least as important as the absolute solubility.

Insolubility in acid gastric juice would be desirable, theoretically, by precluding undesired gastric side effects. In fact, however, it is probably not important, provided that the solution is slow, or that the tannin is taken with food. Of the three types, the acetyltannic acid-U. S. P. is the least soluble in gastric juice; albumin tannate-U. S. P. is fairly soluble, but the solution occurs rather slowly; protan is the most soluble, and the solution occurs more rapidly.

Solubility in sodium bicarbonate solution is, of course, necessary; in fact, the fraction that does not dissolve is merely inert ballast in the therapeutic use that could, however, be compensated by increasing the dose (all three classes contain about half their weight of tannic acid). The most important point is, therefore, the speed of solution. The more rapidly the tannin is dissolved, the more intensely will it act on the upper intestines, and the less on the lower portions. In the case of acetyltannic acid-U. S. P., the ester must also be hydrolyzed before it becomes astringent. The rate of this hydrolysis of acetyltannic acid-U. S. P. is about the same as that of the solution of albumin tannate-U. S. P., in both cases requiring more than three hours for completion. Under clinical conditions, however, a larger part of the albumin tannate-U. S. P. will have been dissolved in the stomach, and it will thus exert a rather stronger action in the duodenum, and probably extend its action slightly less into the lower intestines. Clinically, however, the difference does not seem to be large.

Protan, on the other hand, dissolves completely within half an hour, so that its action would be much greater in the upper and much less in the lower intestines.

Distinctive Differences in Solubility.—All the compounds are somewhat soluble in water: acetyl tannic acid-U. S. P., not more than 7.5 per cent; albumin tannate-U. S. P., not more than 20 per cent; protan about 16 per cent. Artificial gastric juice (acid-pepsin solution) dissolves: acetyl tannic acid-U. S. P., less than 7.5 per cent, in two hours; albumin tannate-U. S. P., less than 25 per cent, in one-half hour; less than 38 per cent, in two hours; protan, about 60 per cent, in one-half hour, about 72 per cent, in two hours. Dilute alkali (1 per cent sodium bicarbonate) hydrolyzes from 33 to 50 per cent of acetyl tannic acid-U. S. P. in one-half hour; 75 per cent is hydrolyzed and 85 per cent dissolved in three hours. Of albumin tannate-U. S. P., it dissolves from 35 to 50 per cent in one-half hour and more than 70 per cent in two hours. Of protan, it dissolves 98 per cent in one-half hour.

Actions and Uses.—The sparingly soluble tannic acid preparations are used in diarrheal affections, particularly those of children. They should be employed not as the principal curative agent, but as an occasional adjunct to the proper physical and dietetic remedies when the discharges are unduly profuse.

As has been explained, acetyltannic acid-U. S. P. and albumin tannate-U. S. P. act at all levels of the intestine. Acetyl tannic acid-U. S. P. might be expected to act somewhat more mildly in the duodenum, and to extend its action somewhat more effectively into the lower intestine; but clinically there does not seem to be much, if any, difference. Protan would tend to expend its action mainly on the upper intestine.

ACETYLTANNIC ACID.—For description see the U. S. Pharmacopeia under Acidum Acetyltannicum.

Actions and Uses.—See preceding article, Tannic Acid Derivatives.

Dosage.—From 0.2 to 0.7 Gm. (3 to 10 grains), four times per day, taken dry on the tongue followed by a swallow of water, or mixed with food, avoiding warm or alkaline liquids.

Tannigen.—A brand of acetyltannic acid-U. S. P.

Manufactured by The Bayer Company, Rensselaer, N. Y. (Winthrop Chemical Company, Inc., New York, distributor). U. S. patent expired.

PROTAN.—Tannin Nucleo-Proteid-Mulford.—A chemical combination of casein with tannic acid containing about 50 per cent tannic acid.

Actions and Uses.—Protan is said to be useful as an intestinal astringent in all forms of diarrhea.

Dosage.—For infants and children, from 0.3 to 0.6 Gm. (5 to 10 grains) every hour; in acute catarrhal diarrhea (cholera morbus), from 1 to 2 Gm. (15 to 30 grains) every one or two hours; in chronic diarrhea, from 1.3 to 2 Gm. (20 to 30 grains) every hour or two hours.

Manufactured by The H. K. Mulford Company, Philadelphia. No U. S. patent. U. S. trademark 38,616.

Friable Tablets, Protan, 5 grains.

Protan and Opium Tablets, No. 1: Opium 0.005 Gm. (1/12 grain) and protan 0.162 Gm. (2½ grains).

Protan is made by adding a solution of tannic acid to an alkaline solution of casein, collecting and drying the precipitate.

It is a light brown powder, tasteless, and free from astringent action on the mouth and stomach; insoluble in water or dilute acids, and does not coagulate albumin or precipitate pepsin or peptones.

When protan is shaken with water and filtered, a colorless solution should be obtained, which should give not more than a faint trace of color with ferric chloride solution, showing absence of more than traces of free (uncombined) tannic acid. The resistance of protan to the action of the gastric juice may be shown by mixing 2 Gm. (dried at 100 C.) with 40 cc. of 0.2 per cent hydrochloric acid containing ten times the theoretical amount of 1 in 3,000 pepsin necessary to digest the protein present, warming to 40 C. for six hours, filtering off the residue, drying and weighing; from 60 to 70 per cent of the amount taken may thus be recovered. The tannin may best be determined by difference, the casein being determined by decomposing it by the Kjeldahl-Gunning method and estimating the nitrogen.

THIOSINAMINE.—Thiosinamina.—Allyl Sulphocarbamide.—Rhodaline.—$(NH_2).CS.NHCH_2.CH:CH_2$.—Allylthiourea.

Actions and Uses. — Thiosinamine is being used against arsphenamine dermatitis (Thiosinamine in the Treatment of Arsphenamine Dermatitis, S. S. Greenbaum, J. A. M. A. **83**:38 [July 5] 1924). This use is still in the experimental stage.

Thiosinamine was originally introduced to promote the absorption of scar-tissue, lymphatic swellings, etc. Clinical opinions as to its efficiency are contradictory; but its restricted use indicates that it has little, if any, value for this purpose.

Although it is usually well borne, except for the bitter taste and acid eructations, it may produce toxic systemic effects (digestive disturbance, lassitude fever, J. A. M. A. **56**:835 [March 18] 1911); and these may set in suddenly after it has been used for a time without toxic effects. In animals, relatively small doses produce severe changes in metabolism and parenchymatous degeneration but without evidence of connective tissue changes. Larger doses impair respiration (Tyrode: *Arch. Internat. Pharmacol.* **19**:195, 1910).

Dosage. — Against arsphenamine dermatitis, Greenbaum recommends 0.2 Gm. dissolved in 6 cc. of distilled water, with the addition of 1 or 2 drops of a 2 per cent solution of glycerin, injected daily, by vein.

Thiosinamine occurs as white, glistening prismatic crystals, having a garlic-like odor and bitter taste. It melts at 70 to 74 C., forming a colorless liquid, but at higher temperatures it yields white vapors, alkaline in reaction to moist litmus paper, and a carbonaceous residue. It is soluble in water (1 part in 17 parts of water), freely soluble in alcohol (1 part in 2 parts of alcohol); not so soluble in ether. Thiosinamine is hydrolyzed by water.

Boil 1 cc. of the saturated aqueous solution with 1 cc. of sodium hydroxide solution for two minutes; acidify with acetic acid and add 1 cc. of lead acetate solution: a black precipitate of lead sulphide forms.

Add 3 cc. of mercuric chloride solution to 1 cc. of the saturated aqueous solution: a white precipitate forms; when heated in the test tube to boiling over a bunsen flame, no discoloration takes place. Add 1 cc. of mercurous nitrate solution to 1 cc. of the aqueous solution: a gray precipitate forms, which, on making the solution ammoniacal, turns yellow, then dark again. Add drop by drop 0.5 cc. of silver nitrate solution (2.5 per cent) to 1 cc. of the saturated aqueous solution; a milky white precipitate forms; then add slowly 3.5 cc. of silver nitrate solution: the precipitate first dissolves in excess of the reagent, then a voluminous white or brownish white precipitate forms. Heat the test tube containing the precipitate over a bunsen flame; a silver mirror forms on the glass.

Ignite about 2 Gm. of thiosinamine, accurately weighed: the ash should not be more than 0.05 per cent.

THORIUM SALTS AND PREPARATIONS

The soluble thorium salts bear a close resemblance to alum in their local astringent and irritant properties. They are not absorbed from the alimentary canal. Hypodermically, they cause local sloughing, and intravenously, they kill by coagulating the blood. The nonprecipitant double salts are practically nontoxic, even intravenously. They are excreted by the kidneys. Thorium salts are fairly radioactive. They have been recommended for local application in malignant diseases, and thorium emanation has been inhaled in phthisis. Reliable evidence as to other therapeutic uses of thorium salts is lacking.

THORIUM NITRATE.—Thorii Nitras.—$Th(N.O_3)_4 + 4H_2O$.—The thorium salt of nitric acid.

Actions and Uses.—See preceding article, Thorium Salts and Preparations.

Thorium nitrate occurs as white crystalline granules or lumps. Very soluble in water and alcohol. On calcination, it yields a voluminous, white oxide, which should amount to from 48 to 50 per cent of the original salt. The aqueous solution dries over sulphuric acid to a crystalline mass.

An aqueous solution gives a white precipitate with ammonium carbonate, the precipitate being completely soluble in an excess of the precipitant. The aqueous solution gives, with caustic alkalis, a voluminous precipitate of the hydroxide, insoluble in an excess of the precipitant. The presence of tartaric or citric acids prevents the precipitation. Potassium ferrocyanide produces an amorphous precipitate.

THYROXIN

Actions and Uses.—Thyroxin (Thyroxinum, U. S. P.) is used essentially for the same purpose as Thyroid-U. S. P., but the dosage may be more accurately determined and results more quickly obtained. It is indicated in cases of diminishing or absent thyroid functioning, such as simple goiter, cretinism and myxedema. The reports of Kendall show that thyroxin affects the pulse rate, blood pressure, nitrogen metabolism, relieves symptoms of myxedema and will produce hyperthyroidism. The most important quantitative measure is the determination of the basal metabolic rate. One milligram (0.001 Gm.) of thyroxin increases the basal metabolic rate in adults approximately 2 per cent. The relation holds for larger amounts, that is, 10 milligrams increases the metabolic rate 20 per cent. It is through the basal metabolic rate that the pharmacologic action of thyroxin can be followed best. When given by mouth or intravenously, there is no immediate effect except occasionally when an increase in pulse rate and respiration occurs, which, however, will soon disappear. After from twenty-four to thirty-six hours, there is a noticeable increase in pulse rate. There may be loss of weight and beginning of nervous manifestations. If the dosage is continued for five or six days, the typical so-called hyperthyroid symptoms will be produced: loss of weight, increased pulse rate with tachycardia, nervous manifestations and a sense of fatigue. With small doses, the harmful effects are not produced and a stimulating effect is manifest in cases of myxedema. With large doses, the symptoms just mentioned are aggravated: the amount of thyroxin required to produce toxic effects is exceedingly small. It has been reported that the maximum effect from a single injection is not reached until the tenth day, the duration of the effects of a single administration of thyroxin being about three weeks.

In some forms of goiter (such as simple adolescent colloid goiter), the function of the thyroid is defective and the administration of thyroxin is indicated; but in most cases of goiter (especially exophthalmic) thyroxin should never be administered.

Dosage.—From 0.2 mg. to 2 mg. Thyroxin should always be given in minimum doses and in each case the optimum amount should be determined by trial. For the exact determination of this dose, the establishment of the basal metabolic rate for each given case is necessary. In general a *normal* adult will show evidences of hyperthyroidism if given as much as 2 mg. per day. A person afflicted with high-grade myxedema requires from 1.5 to 2 mg. per day; a small cretin requires from 0.2 to 0.4 mg. every day or every other day.

Thyroxin may be administered either by intravenous injection or by mouth. In those cases in which thyroxin is not absorbed quantitatively when given by mouth it may be given intravenously according to the following directions: Place a known amount of pure crystalline thyroxin—from 1 to 10 mg.—in a small sterile test tube, such as is used for the Wassermann test. Add 1 drop of 10 per cent sodium hydroxide solution and about 1 cc. of water. Warm and agitate the solution until the crystals are dissolved, and then sterilize by placing the tube in boiling water. Transfer the solution to a sterile hypodermic syringe, rinse out the test tube with 1 cc. of sterile distilled water, which is added to the syringe, and then inject the contents of the syringe intravenously.

In many cases, after symptoms of hypothyroidism have disappeared, remarkably small doses suffice to keep the patient in an almost normal state. The patient should be careful of exertion and should take sufficient protein in the diet to compensate for increased loss of nitrogen from the action of the drug.

THYROXIN CRUDE.—The partially purified disodium salt of thyroxin, approximately 25 per cent admixed with the acid-insoluble humus-like products of protein hydrolysis.

Actions and Uses.—The same as those of thyroxin, except that it is not to be used for injection. In certain individuals in whom the thyroxin equivalent is not absorbed quantitatively, the pure crystalline thyroxin should be given intravenously (see under thyroxin).

Dosage.—Thyroxin crude is supplied in the form of tablets for oral administration, representing a stated weight of thyroxin. Thyroxin crude must not be administered intravenously.

Manufactured by E. R. Squibb & Sons, New York, by license of the University of Minnesota. U. S. patents 1,392,767 (Oct. 4, 1921; expires 1938), and 1,392,768 (Oct. 4, 1921; expires 1938).

Thyroxin Tablets, 0.2 mg.: Each tablet contains thyroxin crude, equivalent to 0.2 mg. thyroxin.

Thyroxin Tablets, 0.4 mg.: Each tablet contains thyroxin crude equivalent to 0.4 mg. thyroxin.

Thyroxin Tablets, 0.8 mg.: Each tablet contains thyroxin crude, equivalent to 0.8 mg. thyroxin.

Thyroxin Tablets, 2.0 mg.: Each tablet contains thyroxin crude, equivalent to 2.0 mg. thyroxin.

Thyroid glands of animals are hydrolyzed by treatment with sodium hydroxide solution. The resulting soaps and alkali insoluble materials are removed. The clarified hydrolysate is precipitated with acid and filtered. The precipitation is twice repeated and the residue finally redissolved in a slight excess of sodium carbonate solution, dried and powdered. The thyroxin content is determined by the assay described below and the product made into tablets with sucrose and lactose as vehicles.

Thyroxin crude is a light brown powder having a characteristic odor and an alkaline taste. It is soluble in water; decomposed by acids. The following method may be applied for the assay of thyroxin tablets:

Weigh accurately five or ten tablets. Grind finely the tablets and weigh out a sample of the powdered thyroxin for analysis; place over sulphuric acid in a desiccator for twenty-four hours and determine loss in weight. Deliver the dried sample in a beaker and add 10 cc. sodium hydroxide solution, 30 per cent. Dissolve the sample by "working" it with the aid of a glass rod; add 50 cc. of water. Filter the solution into a small beaker, wash the original beaker and filter paper with sodium hydroxide test solution. Make the filtrate faintly acid with dilute sulphuric acid solution; filter off the precipitate and wash it. Determine the iodine content in the precipitate according to the method of Kendall (*Jour. Biol. Chem.* **19**: 252, 1914), and calculate the amount of thyroxin in the dried specimen and in tablets. (The iodine in the precipitate is thyroxin iodine; any iodine in the filtrate is from other iodine-containing compounds, and is physiologically inactive. Thyroxin tablets-Squibb contain a small amount of humus-like substance resulting from the hydrolysis of the protein.)

TRIBASIC CALCIUM PHOSPHATE.—Calcii Phosphas Tribasicus.—Tertiary Calcium Phosphate, $Ca_3(PO_4)_2$. Tribasic calcium phosphate contains approximately 85 per cent of $Ca_3(PO_4)_2$.

Actions and Uses.—Tribasic calcium phosphate has been proposed for use as an antacid. It has the advantage over alkaline hydroxides such as magnesium hydroxide and alkali carbonates such as sodium bicarbonate, in that, being insoluble, it neutralizes the excess of acid in the stomach but does not produce systemic alkalization. It has been claimed that tribasic calcium phosphate is somewhat constipating.

Dosage.—From 1 to 5 Gm. (15 to 75 grains).

Tribasic calcium phosphate occurs as a white, odorless and tasteless powder. It is almost insoluble in water but is readily soluble in diluted mineral acids. Water agitated with tribasic calcium phosphate is neutral or acquires a slight alkaline reaction to litmus paper.

Dissolve 0.2 Gm. of tribasic calcium phosphate in 5 cc. of diluted hydrochloric acid, add drop by drop ammonia water until a precipitate forms, add 1 cc. of acetic acid, followed by 1 or 2 cc. of ammonium oxalate solution: a white precipitate forms. Dissolve 0.2 Gm. of tribasic calcium phosphate in a slight excess of diluted nitric acid and add ammonium molybdate solution: a yellow precipitate forms which is soluble in ammonia water. Mix 0.2 Gm. of tribasic calcium phosphate with about 5 cc. of water, then add 20 cc. of neutral solution of silver nitrate (1 in 20) and agitate the mixture for about two minutes, keeping protected from light: the liquid is neutral to litmus paper (*distinction from dibasic phosphate*), and the precipitate is of a pure yellow color, free from brown or gray (*uncombined calcium oxide*). A solution of 0.2 Gm. of the salt in 10 cc. of water and just sufficient hydrochloric acid is not darkened by the addition of an equal volume of hydrogen sulphide water (*heavy metals*). Mix 0.5 Gm. of the salt with 3 cc. of water and immediately add 3 cc. of diluted hydrochloric acid: not more than a few gas bubbles should be evolved (*carbonate*). Dissolve 0.2 Gm. of tribasic calcium phosphate in 10 cc. of diluted nitric acid and add 1 cc. of silver nitrate solution: not more than a slight turbidity results (*chloride*). To a solution of 0.5 Gm. of the salt in 10 cc. of diluted hydrochloric acid, filtered if necessary, add a few drops of diluted sulphuric acid: no turbidity is produced in ten minutes (*barium*). Dissolve 0.2 Gm. of tribasic calcium phosphate in 5 cc. of diluted nitric acid, add a few cubic centimeters of sulphuric acid and heat until fumes of sulphur trioxide are evolved; add 10 cc. of sulphurous acid solution, evaporate until the solution is free from sulphur dioxide, dilute the evaporated solution to 5 cc.: this meets the U. S. P. X limit for arsenic. Digest 2 Gm. of the salt with 100 cc. of water for one-half hour on a steam bath, cool, add sufficient water to restore the original volume, stir well, filter, evaporate 50 cc. of the filtrate to dryness in a porcelain dish, and ignite the residue gently: the weight of the residue does not exceed 0.005 Gm. (*soluble salts*). Dissolve 0.2 Gm. of tribasic calcium phosphate in the smallest possible amount of diluted hydrochloric acid, filter, wash, make the filtrate up to 49 cc. and add 1 cc. of barium chloride solution: the turbidity produced should not be greater than is apparent in a similarly made up control tube using 2 cc. fiftieth-normal sulphuric acid in place of the calcium phosphate (see U. S. P. X, page 462). Agitate 1 Gm. of tribasic calcium phosphate with 30 cc. water for five minutes, filter and add to the filtrate 2 drops phenolphthalein solution: the pink color, if any, is completely discharged by one drop of tenth-normal acid (*uncombined calcium oxide*).

Dissolve about 0.2 Gm. tribasic calcium phosphate, accurately weighed, in a mixture of 25 cc. of water and 10 cc. nitric acid, filter and wash if not entirely soluble, add ammonia water until a slight precipitate is produced, then dissolve the precipitate by the addition of 1 cc. of nitric acid, cool or heat the solution to about 50 C., add 75 cc. of ammonium molybdate solution, and allow to remain at this temperature for thirty minutes, stirring occasionally, filter at once, wash once or twice with water by decantation, using 30 to 40 cc. each time, transfer the precipitate to the filter and wash with cold water until the washings cease to react acid with litmus paper, transfer the precipitate and filter to the precipitating vessel, add 50 cc. of half-normal sodium hydroxide, agitate until the precipitate is dissolved and then titrate the excess of alkali with half-normal sulphuric acid, using 3 drops of phenolphthalein solution as indicator. Each cubic centimeter of half-normal sodium hydroxide consumed corresponds to 0.002066 Gm. $PO_4^{\equiv}$. The amount of phosphate ($PO_4^{\equiv}$) should not be less than 52 per cent.

Dissolve about 0.5 Gm. of tribasic calcium phosphate, accurately weighed, in diluted hydrochloric acid; filter if the product is not entirely soluble, wash, and add ammonia water until a permanent precipitate just forms; add 2 per cent citric acid solution until the precipitate just dissolves and then add 50 cc. more; make up to 200 cc.; add an excess of ammonium oxalate solution, allow to stand one hour on the steam bath, filter, wash, dissolve the precipitate in diluted hydrochloric acid, then add ammonia water until alkaline, and a few cubic centimeters of ammonium oxalate solution; allow the mixture to stand on the steam bath an hour, filter, wash, dry and ignite to constant weight; calculate the weight of the calcium oxide to calcium (Ca): the percentage of calcium found multiplied by the factor 1.581 (Ca to $PO_4^{\equiv}$ in $Ca_3(PO_4)_2$) should correspond with the percentage of phosphate ($PO_4^{\equiv}$) found plus or minus 2.5 per cent.

On ignition, tribasic calcium phosphate loses not more than 8 per cent of its weight.

Calcium Phosphate Tribasic-Merck.—A brand of tribasic calcium phosphate-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

TRIBASIC MAGNESIUM PHOSPHATE. — Magnesii Phosphas Tribasicus.—Tertiary Magnesium Phosphate, $Mg_3(PO_4)_2.7H_2O$. Tribasic magnesium phosphate contains approximately 70 per cent $Mg_3(PO_4)_2$.

Actions and Uses.—Tribasic magnesium phosphate has been proposed for use as an antacid. It has the advantage over alkaline hydroxides such as magnesium hydroxide and alkali carbonates such as sodium bicarbonate in that, being insoluble, it neutralizes the excess of acid in the stomach, but does not produce systemic alkalization. It has been claimed that tribasic magnesium phosphate has a laxative action.

Dosage.—From 1 to 5 Gm. (15 to 75 grains).

Tribasic magnesium phosphate occurs as a white, odorless and tasteless powder. It is almost insoluble in water, but it is readily soluble in diluted mineral acids. Water agitated with tribasic magnesium phosphate is neutral or acquires a slightly alkaline reaction to litmus paper.

Dissolve about 0.2 Gm. of tribasic magnesium phosphate in a slight excess of diluted nitric acid and add ammonium molybdate solution: yellow precipitate forms which is soluble in ammonia water. Mix 0.2 Gm. of tribasic magnesium phosphate with about 5 cc. of water, then add 20 cc. of neutral solution of silver nitrate (1 in 20) and agitate the mixture for about two minutes, keeping protected from light: the liquid is neutral to litmus paper (*distinction from dibasic phosphate*), and the precipitate is of a pure yellow color, free from brown or gray (*uncombined magnesium oxide*). A solution of 0.2 Gm. of the salt in 10 cc. of water and just sufficient hydrochloric acid is not darkened by the addition of an equal volume of hydrogen sulphide water (*heavy metals*). Mix 0.5 Gm. of the salt with 3 cc. of water and add 3 cc. of diluted hydrochloric acid: not more than a few gas bubbles should be evolved (*carbonate*). Add 5 cc. of sodium hydroxide solution to 0.5 Gm. of tribasic magnesium phosphate solution and heat: the odor of ammonia is not evolved (*magnesium ammonium phosphate*). To a solution of 0.5 Gm. of the salt in 10 cc. of diluted hydrochloric acid, filtered if necessary, add a few drops of diluted sulphuric acid: no turbidity is produced in ten minutes (*barium*). Dissolve 0.2 Gm. of tribasic magnesium phosphate in 5 cc. of diluted nitric acid, add a few cubic centimeters of sulphuric acid and heat until fumes of sulphur trioxide are evolved; add 10 cc. of sulphurous acid solution, and evaporate until the solution is free from sulphur dioxide; dilute the evaporated solution to 5 cc.: this meets the U. S. P. X limits for arsenic. Add 30 cc. of water to 1 Gm. of the salt; follow with 5 cc. of hydrochloric acid, warm if necessary until the salt is dissolved, cool, add ammonia water in small portions until a permanent precipitate is just produced and then add 5 cc. acetic acid: not more than a slight quantity remains undissolved (*aluminum, iron, etc.*). Filter the solution if not clear and add 5 cc. ammonium oxalate: not more than a slight turbidity is produced (*calcium*). Dilute 1 cc. of the solution to 200 cc. and add ammonia water until alkaline to litmus paper: a white crystalline precipitate gradually appears. When tribasic magnesium phosphate is assayed for chloride and sulphate according to the method described in the U. S. P. X, page 462, their sum should not exceed 0.5 per cent. Digest 2 Gm. of the salt with 100 cc. of water for one-half hour on a steam bath, cool, add sufficient water to restore the original volume, mix and filter; evaporate 50 cc. of the filtrate to dryness and ignite gently: the weight of the residue does not exceed 0.015 Gm. (*soluble salts*). Agitate 1 Gm. of tribasic magnesium phosphate with 20 cc. of water for five minutes, filter, and add to the filtrate 2 drops phenolphthalein solution: the pink color, if any, is completely discharged by one drop of tenth-normal acid (*uncombined magnesium oxide*).

Determine the phosphate content of tribasic magnesium phosphate by the method given under tribasic calcium phosphate. **The amount of phosphate ($PO_4^{\equiv}$) should not be less than 50 per cent.**

Dissolve about 0.5 Gm. of tribasic magnesium phosphate, accurately weighed, in 25 cc. of diluted hydrochloric acid; add ammonia water in small portions until a permanent precipitate is just produced and redissolve the precipitate by the addition of acetic acid; if the solution is not clear, filter and wash; add to the solution 10 cc. of sodium phosphate T. S., then render strongly alkaline by the addition of stronger ammonia water; allow the mixture to stand twenty-four hours; filter on a tared Gooch crucible and wash the precipitate with diluted ammonia water (1 volume of ammonia water diluted with 19 volumes of water) until the washings cease to give a reaction for chloride, ignite and weigh: **the percentage of magnesium found multiplied by 2.605 (factor Mg to $PO_4^{\equiv}$ in $Mg_3(PO_4)_2$) should correspond to the percentage of phosphate ($PO_4^{\equiv}$) found plus or minus 1.5 per cent.**

On ignition it loses from 25 per cent to 30 per cent of its weight.

Magnesium Phosphate Tribasic-Merck.—A brand of tribasic magnesium phosphate-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

URETHANES (CARBAMATES), UREA AND UREIDS

The starting-point of this group is urea, which is carbamide, $NH_2.CO.NH_2$. By the addition of a molecule of water to this compound, we have ammonium carbamate, $NH_2CO ONH_4$; substitution of ethyl for ammonium yields ethyl carbamate (urethane), $NH_2CO.O(C_2H_5)$. By substitution of phenyl for hydrogen, we get $NH(C_6H_5).CO.O(C_2H_5)$, phenyl urethane or phenyl ethyl carbamate. By substituting for the ethyl of urethane the radical of methyl propyl carbinol, we get methyl propyl carbinol urethane, $NH_2.CO.O.CH(CH_3)CH_2.CH_2.CH_3$ or hedonal.

Urethanes are diuretic and hypnotic agents. They are oxydized in the system to carbon dioxide and urea. Urethane is a comparatively feeble hypnotic.

ADALIN.—See Bromine Derivatives.

BARBITAL.—See Barbital and Barbital Compounds.

LUMINAL.—See Barbital and Barbital Compounds.

UREA.—Urea.—$CO(NH_2)_2$.—The diamide of carbonic acid

Actions and Uses.—Urea is an active diuretic: it is rapidly eliminated and is not poisonous. It is useless in the treatment of tuberculosis, and has no important solvent action on urinary calculi. It may be employed when diuresis is indicated, though it appears irrational in any renal disease characterized by retention of nitrogen.

Dosage.—From 0.5 to 4 Gm. (10 to 60 grains). Urea is given in solution, or it may be enclosed in cachets.

Urea occurs as colorless, transparent prismatic crystals, almost odorless and having a cooling saline taste. It is somewhat hygroscopic It is soluble in water (1 in 1), more readily in hot water; soluble in alcohol (about 1 in 10) and (1 in 1) in boiling alcohol. It is insoluble in ether and chloroform' it fuses at 132 C., evolving ammonia and ammonium cyanate. Kept at 150 C., for some time, most of it is converted to biuret. If the temperature is raised to 170 C., the biuret evolves ammonia and is converted to cyanuric acid. Heated with water under pressure, it is decomposed into ammonium carbonate. It is not alkaline, but is a weak base and though a diamide, forms salts like a monacid base; these are acid to litmus. By hydrolysis it is converted into ammonia and carbon dioxide. Nitric and oxalic acids produce precipitates when added to concentrated solutions of urea.

Urea-Merck.—A brand of urea-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.

VIOSTEROL

Investigators working with various sterols discovered that ergosterol (originally derived from ergot but now obtained from other substances, mainly yeast), in crystalline form or in solution, when subjected to ultraviolet radiation develops an antirachitic (vitamin D) potency enormously greater than that of cod liver oil. For therapeutic use the ergosterol after irradiation is usually dissolved in a vegetable oil. The Council has adopted the term viosterol to designate irradiated ergosterol, and viosterol in oil to designate a preparation containing this substance dissolved in oil. The Council has also provisionally adopted the qualifying phrases 100 D, 5 D, etc., to designate the vitamin D potency of the various preparations as multiples of the vitamin D potency of good cod liver oil. The potency of viosterol preparations is measured by the methods used for determining the vitamin D potency of cod liver oil.

Viosterol is for use in prophylaxis and treatment of rickets and, experimentally, in other conditions arising from faulty calcium and phosphorus assimilation. It should be borne in mind that viosterol does not contain vitamin A and that harm from hypercalcemia may result from the use of too large doses of the substance.

COD LIVER OIL WITH VIOSTEROL (See under Cod Liver Oil and Cod Liver Oil Preparations).

VIOSTEROL IN OIL 100 D.—Irradiated Ergosterol in Oil.—Activated Ergosterol in Oil.—Viosterol dissolved in a vegetable oil and standardized to contain 1,333 rat units of vitamin D in each Gm., this strength being 100 times that of a potent cod liver oil used as a standard.

Actions and Uses.—See preceding article, Viosterol.

Dosage.—Daily prophylactic dose for the average infant and child, 8 to 10 drops (0.1233 to 0.1666 cc.: 2⅔ to 3⅓ minims); for the premature and rapidly growing infant, 15 drops (0.25 cc.: 5 minims); daily curative dose, 15 to 20 drops (0.25 to 0.333 cc.: 5 to 7 minims); in severe cases and for adults, doses in excess of 20 drops may be given. The marketed preparations are accompanied by a standard dropper designed to deliver 3 drops to the minim.

Viosterol in oil 100 D is standardized by comparison with a potent cod liver oil containing in each 0.75 mg. 1 rat unit of vitamin D, the rat unit being defined as that amount of vitamin D which, when uniformly distributed into the standard vitamin D deficient diet—ration 2965, *Jour. Biol. Chem.* **64**: 263, 1925—will produce a narrow and continuous line of calcium deposits in the metaphyses of the distal ends of the radii and ulnae of standard rachitic rats.

Viosterol in Oil 100 D-Abbott.—A brand of viosterol in oil 100 D, N. N. R.

Manufactured by The Abbott Laboratories, North Chicago, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) by license of the Wisconsin Alumni Research Foundation.

Viosterol in Oil 100 D-Abbott is prepared by dissolving ergosterol in anhydrous, peroxide free ether-U. S. P.; the solution is filtered, placed in transparent quartz containers with reflux condensers, and exposed to ultraviolet rays at a determined distance and intensity for a determined length of time. The irradiated ergosterol, freed of ether and dissolved in sesame oil, is biologically assayed and adjusted to have the potency of viosterol in oil 100 D, N. N. R.

Mead's Viosterol in Oil 100 D.—A brand of viosterol in oil 100 D, N. N. R.

Manufactured by Mead Johnson & Co., Evansville, Ind., under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) by license of the Wisconsin Alumni Research Foundation.

Mead's viosterol in oil 100 D is prepared by exposing, under reflux, an ether solution of ergosterol and an antioxidant to the radiation from an iron-cored-carbon arc. The antioxidant is then removed, the solvent evaporated to dryness, and the residue dissolved in maize oil. The resulting solution is biologically assayed and adjusted to have the potency of viosterol in oil 100 D, N. N. R. The final dilution is also biologically tested.

Parke, Davis & Co.'s Viosterol in Oil 100 D.—A brand of viosterol in oil 100 D, N. N. R.

Manufactured by Parke, Davis & Co., Detroit, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) by license of the Wisconsin Alumni Research Foundation.

Parke, Davis & Co.'s Viosterol in Oil 100 D is prepared by dissolving crystalline ergosterol in purified ether to a definite concentration; the solution is then irradiated by exposure to ultraviolet rays from a lamp of the quartz mercury arc burner type; after irradiation the ether is recovered and the irradiated ergosterol is dissolved in maize oil. The final dilution and concentration is based upon the biological assay and is adjusted to have the potency of viosterol in oil 100 D, N. N. R.

Viosterol in Oil 100 D-Squibb.—A brand of viosterol in oil 100 D, N. N. R.

Manufactured by E. R. Squibb & Sons, New York, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) by license of the Wisconsin Alumni Research Foundation.

Viosterol in Oil 100 D-Squibb is prepared by dissolving ergosterol in ether; the solution is then irradiated by exposure to ultraviolet rays; after assay of the irradiated ergosterol for its antirachitic potency, it is dissolved in maize oil and adjusted to have the potency of viosterol in oil 100 D, N. N. R.

XANTHINE DERIVATIVES

Structure and Relations.—Caffeine, theobromine and theophylline are methyl xanthines, derived from xanthine by the introduction of two or three methyl radicals into a corresponding number of NH_2 groups. As these may occupy various positions in the xanthine nucleus, a considerable number of methyl xanthines exist, naturally or by synthesis, differing quantitatively in pharmacologic activity. Those named, however, are the only ones of therapeutic importance, namely, caffeine = 1 : 3 : 7 trimethylxanthine; theobromine = 3 : 7 dimethylxanthine; and theophylline = 1 : 3 dimethylxanthine.

Caffeine is usually obtained from tea or coffee; theobromine is obtained from cacao, or is made synthetically. Theophylline occurs in nature but in amounts too small to be commercially available. It is prepared synthetically. Theocin is a proprietary name for synthetic theophylline.

Actions.—Theobromine and theophylline surpass caffeine in their diuretic, and perhaps in cardiac and muscular actions. They are, therefore, generally preferred in cardiac edemas, etc., since they are equally, or more, effective, more prompt, and largely avoid the unpleasant side effects (insomnia, nervousness, gastric disturbance) which often interfere with the use of caffeine in adequate doses. This freedom from side effects holds true, particularly of theobromine. Theophylline surpasses theobromine in diuretic efficacy, but its action is probably not so lasting; it may produce gastric disturbances; renal irritation has been reported. Theobromine is, therefore, generally preferred, sometimes preceded for a few days by theophylline. If central stimulation is desired, caffeine must be used.

Compounds.—The slight solubility of free theobromine and theophylline limits their usefulness. They are therefore used almost exclusively in the form of the readily soluble double salts (such as theobromine sodium-salicylate, U. S. P.), which they form with a considerable number of compounds. There is no reason to suppose that the particular salt used to procure the solubility has any material influence on the action. The dosage of these added compounds is also generally too small to produce therapeutic effects. It may, therefore, be assumed that the various commercial combinations are strictly equivalent.

Theobromine and Theobromine Compounds

THEOBROMINE. — Theobromina. — 3.7-Dimethylxanthine. —$C_5H_2(CH_3)_2.O_2N_4$. A base occurring in *Theobroma cacao;* also made synthetically.

Actions and Uses.—The uses of theobromine are similar to those of caffeine, but its action is said to be relatively greater on the heart and muscles and also as a diuretic. It does not act so powerfully on the central nervous system.

It is used as a diuretic. The great obstacle to its use has been its insolubility and the consequent uncertainty of the degree of its absorption. It is liable to produce gastric disturbances.

Dosage.—From 0.35 to 0.5 Gm. (5 to 8 grains).

Theobromine occurs as colorless, rhombic needles or as a white crystalline powder, odorless, bitter, and permanent in the air.

Theobromine is slightly soluble in water, alcohol, ethyl acetate and chloroform, and insoluble in petroleum ether. It is soluble in aqueous solutions of the alkalis.

Dissolve about 0.01 Gm. of theobromine in 1 cc. of hyrochloric acid in a porcelain dish, add 0.1 Gm. of potassium chlorate, evaporate the mixture to dryness on a water bath and invert the dish over a vessel containing a few drops of ammonia water: the residue acquires a purple color, which is destroyed by fixed alkalis.

Add about 0.2 Gm. of theobromine to 3 cc. of water containing a few drops of diluted sulphuric acid and heat the mixture; cool, filter and add a few drops of tanic acid solution: a white precipitate is formed which is soluble in an excess of the reagent.

Dissolve about 0.1 Gm. of theobromine in 50 cc. of very dilute ammonia water by the aid of a gentle heat; add an excess of silver nitrate solution; agitate the mixture and warm on the water bath: a white, crystalline precipitate forms on standing.

The aqueous solution of theobromine (1 in 2,000) is not precipitated by iodine solution or by potassium mercuric iodide solution (absence of most *foreign alkaloids*).

Shake about 1 Gm. of theobromine, accurately weighed, with 10 cc. of benzol in a glass-stoppered container; allow to stand over night, filter through dry filter paper, reject the first 5 cc. of filtrate, evaporate the succeeding 3 cc. of the filtrate, dry the residue, if any, at 100 C., and weigh: the residue should weigh not more than 0.001 Gm. (limit of *caffeine*). Dry about 1 Gm. of theobromine, accurately weighed, to constant weight at 100 C.: the loss does not exceed 3 per cent of the weight taken (limit of *moisture*). Incinerate about 0.5 Gm. of theobromine, accurately weighed: the ash does not exceed 0.1 per cent. Dissolve about 0.2 Gm. of theobromine in 5 cc. of sulphuric acid: not more than a faint yellow color is produced within five minutes (*organic impurities*).

Theobromine-Merck.—A brand of theobromine-N. N. R.
Merck & Co., Inc., Rahway, N. J., distributor.

THEOBROMINE SODIUM-ACETATE.—**Theobrominae Sodio-Acetas.**—A hydrated double salt of theobromine sodium and sodium acetate, containing not less than 63 per cent of theobromine, corresponding to about 80 per cent of the anhydrous double salt.—$NaC_7H_7O_2N_4+NaC_2H_3O_2$.

Actions and Uses.—Theobromine sodium-acetate acts like theobromine, over which it has the advantages of greater solubility and of being well tolerated by the stomach. While inferior in diuretic power to theophylline (which see), it is said to have greater power in sustaining the diuresis produced.

Dosage.—From 0.5 to 1 Gm. (8 to 15 grains), preferably in wafers or capsules. If in solution, this should be freshly prepared (with peppermint water), without sugar or mucilage.

Theobromine sodium-acetate is a white, finely crystalline powder, odorless and bitter. It is soluble in cold water; slightly soluble in cold alcohol; more so in hot alcohol. Its aqueous solutions are strongly alkaline toward phenolphthalein and litmus. It is quite hygroscopic, and in aqueous solution when exposed to air it gradually splits up into its components through absorption of carbon dioxide and becomes incompletely soluble. Its aqueous solution is precipitated and decomposed by carbon dioxide and by acids. It forms a bluish-white precipitate with silver nitrate solution, a blue precipitate with copper sulphate solution, and a white one with tartar emetic solution. It is not readily precipitated by mercuric potassium iodide solution or by iodine solution. It is incompatible with carbonated beverages, acids, saccharine and mucilaginous liquids, and most of the alkaloidal reagents.

To 10 cc. of an aqueous solution of theobromine sodium-acetate (1 in 50) add 2 cc. of diluted nitric acid, filter and add a few drops of silver nitrate solution to the filtrate: not more than an opalescence results (*limit of chloride*).

Dry about 1 Gm. of theobromine sodium-acetate, accurately weighed, to constant weight at 100 C.: the loss does not exceed 20 per cent.

Dissolve about 1 Gm. of theobromine sodium-acetate, accurately weighed, which has previously been dried to constant weight at 100 C. in 100 cc. of hot water, add phenolphthalein solution and titrate with normal hydrochloric acid to the disappearance of the pink color: not more than 3.7 cc. of normal acid should be required for each gram.

Dissolve about 0.25 Gm. of theobromine sodium-acetate, accurately weighed, which has been previously dried to constant weight at 100 C., in 100 cc. of hot water, add a few drops of potassium chromate solution and titrate the solution while hot with tenth-normal silver nitrate to the formation of a reddish color; the tenth-normal silver nitrate consumed corresponds to at least 63 per cent of theobromine.

Agurin.—A brand of theobromine sodium-acetate-N. N. R. Marketed in the form of tablets only.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (Winthrop Chemical Company, Inc., New York). U. S. trademark 36,018.

Theobromine and Sodium Acetate-Merck.—A brand of theobromine sodium-acetate-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

Theobromine and Sodium Acetate-Roche.—A brand of theobromine sodium-acetate-N. N. R.

Manufactured by F. Hoffmann-La Roche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J.).

THEOCALCIN.—A double salt or mixture of calcium theobromine ($[C_7H_7O_2N_4]_2Ca$) and calcium salicylate ($[C_7H_5O_3]_2Ca$). It contains not less than 44 per cent of theobromine.

Actions and Uses.—Theocalcin acts like theobromine, over which it has the advantage of greater solubility. It is, however, less soluble than the official theobromine sodio-salicylate: on this account it is claimed to be less likely to produce gastric irritation.

Dosage.—Average dose, from 0.5 to 1 Gm. (7 to 15 grains) three times a day.

Manufactured by E. Bilhuber, Inc., New York. U. S. patent 1,547,698 (July 28, 1925; expires 1942). U. S. trademark No. 194,898.

Theocalcin Tablets 7½ Grains.

Theocalcin is a white, amorphous powder, having a saline taste. It is partly soluble in water.

An aqueous solution of theocalcin is alkaline to phenolphthalein. An aqueous solution of theocalcin (1 in 100), slightly acidulated with acetic acid, becomes violet on the addition of ferric chloride solution. Transfer about 0.05 Gm. of theocalcin to a test tube, add 3 cc. of diluted acetic acid and heat to boiling; cool the contents of the test tube, filter and to the filtrate add 0.5 cc. of ammonium oxalate solution: a precipitate forms, which dissolves on addition of 1 cc. of diluted hydrochloric acid. To about 0.05 Gm. of the precipitate obtained in the assay for theobromine, add 1 cc. of hydrochloric acid and about 0.1 Gm. of potassium chlorate and evaporate to dryness on a water bath: a reddish yellow residue remains, which becomes purple when moistened with a drop of ammonia water.

Dried to constant weight at 110 C., theocalcin loses not more than 5 per cent (*water*). Treat 0.1 Gm. theocalcin with 2 cc. of sulphuric acid: no effervescence occurs (*carbonate*) nor is more than a slight color produced (*readily carbonizable substances*). Mix 1 Gm. of theocalcin with 10 cc. of distilled water, add a few cubic centimeters of sodium hydroxide solution (filter if necessary) and shake the mixture with 10 cc. of chloroform separate the chloroform layer, evaporate it to dryness on a water bath and dry to constant weight at 80 C.: the weight of the residue so obtained does not exceed 0.005 Gm. (*caffeine*).

Suspend about 2 Gm. of theocalcin, accurately weighed, in 75 cc. of water and add diluted hydrochloric acid until the solution is acid to phenolphthalein. Warm gently, then add sodium carbonate solution until the calcium is completely precipitated, avoiding a large excess. Filter off the calcium carbonate; evaporate the combined filtrate and washings on a steam bath to 20 cc. Add diluted hydrochloric acid, drop by drop, until just acid (to phenolphthalein), then dilute ammonia water until slightly alkaline. Allow to stand at from 20 to 25 C. for three hours, stirring occasionally. Transfer the precipitate of theobromine to a tared gooch crucible. Wash the precipitate and filter with four successive portions of 5 cc. each of ice cold distilled water and dry to constant weight at 100 C. To the weight of the precipitate thus obtained, add 0.14 Gm. The total weight corresponds to not less than 44 per cent of the weight of theocalcin taken. About 0.2 Gm. of the precipitate obtained in the assay for theobromine volatilizes when slowly heated, leaving only a negligible residue.

Theophylline and Theophylline Compounds

THEOPHYLLINE.—For description see the U. S. Pharmacopeia and Useful Drugs under Theophyllina.

Theocin.—A brand of theophylline-U. S. P. prepared synthetically.

Manufactured by The Bayer Company, Inc., Rensselaer, N. Y. (Winthrop Chemical Co., New York, distributor). U. S. patent 716,994 (issued Dec. 30, 1902; expired). U. S. trademark 39,135.

Theocin is obtained by heating the monoformyl derivative of 1,3-dimethyl-4.5-diamido-2,6-dioxy-pyrimidin with alkalis resulting in the preliminary formation of an alkaline salt of the formyl compound. On further heating, this splits off one molecule of water, forming the alkali salt of theocin. Subsequent treatment with acids liberates theocin.

THEOPHYLLINE SODIO-ACETATE. — Theophyllinæ Sodio-Acetas.—$NaC_7H_7O_2N_4+NaC_2H_3O_2+H_2O$.—A double salt of sodium acetate and 1.3-dimethylxanthinesodium (theophyllinsodium).

Dosage.—From 0.2 to 0.35 Gm. (3 to 5 grains), best given after meals.

It is a white crystalline powder, containing about 60 per cent of anhydrous theophylline. It dissolves in about 20 parts of water at 25 C., but is insoluble in alcohol or ether.

Theocin Soluble.—Theocin Sodium Acetate.—A brand of theophylline sodio-acetate-N. N. R.

Tablets Theocin Soluble, 2½ grains.

Manufactured by the Bayer Co., Inc., Rensselaer, N. Y. (Winthrop Chemical Co., New York, distributor). U. S. patent 716,994 (issued Dec. 30, 1902; expired). U. S. trademark 39,135.

ZINC COMPOUNDS

The essential action of salts of zinc, like those of copper and lead, is that of an astringent or corrosive. The action of these salts being largely proportional to the concentration, zinc chloride in strong solution has been used as an escharotic, fairly strong solutions of zinc sulphate as an emetic, weaker solutions of zinc sulphate and zinc acetate as astringent and antiseptic applications to the mucous membranes of the eye, urethra, etc., while the insoluble zinc oxide is used externally as a mild antiseptic and astringent. Zinc oxide was thought to act on the nervous system; but this theory is probably incorrect, and the internal use of zinc oxide has been practically abandoned.

Various zinc salts containing therapeutically active acid radicals or anions have been used in medicine; thus in zinc permanganate the oxidizing action of the permanganate radical is influenced beneficially, it is claimed, by the astringent action of the zinc. Zinc peroxide is described under Metallic Peroxides.

ZINC PERMANGANATE. — Zinci Permanganas. — $Zn(MnO_4)_2+6H_2O$.—The zinc salt of permanganic acid. It should contain not less than 90 per cent of zinc permanganate.

Actions and Uses.—Zinc permanganate resembles the potassium salt in its oxidizing properties, but is more astringent. It is antiseptic. It is used chiefly in urethritis, either as an injection or as a urethral douche.

Dosage.—Locally, 1 part to 4,000 (1 grain in 8 fluidounces) 1.3 Gm. of zinc permanganate is equal in permanganate content to 1 Gm. of potassium permanganate.

Tablets Zinc Permanganate, 1 grain, Mulford.
Prepared by the H. K. Mulford Company, Philadelphia.

Zinc permanganate occurs in dark brown, nearly black, lustrous deliquescent crystals, or crystalline masses. It is readily soluble in water (1 in 3), generally leaving a slight residue. Aqueous solutions decompose in air, but are permanent if kept in well-closed bottles, protected from light. When heated slowly, it loses water of crystallization (25.46 per cent) and oxygen, leaving a residue of zinc manganite. If heated quickly, it gives off pink vapors, or more properly, a fine dust of manganese trioxide. Zinc permanganate gives up oxygen more easily than does the potassium salt, hence great care should be taken in bringing it in contact with easily oxidizable substances.

Zinc permanganate should be almost completely soluble in water. The color of the solution is discharged by alcohol, hydrogen sulphide, ferrous sulphate, oxalic acid, or hydrogen dioxide, especially if the solution is first rendered acid with sulphuric acid.

If 1 Gm. of the salt is dissolved in 50 cc. of water and 5 cc. of alcohol is added, a colorless solution must be obtained after boiling and filtering; if a small part of the latter, acidified with nitric acid, is tested with silver nitrate solution for chloride and with barium chloride solution for sulphate, not more than traces of either will be indicated.

If zinc permanganate is examined by the method given below, the residual titration will indicate the presence of not less than 90 per cent zinc permanganate ($Zn(MnO_4)_2.6H_2O$). From 0.1 to 0.2 Gm. of substance is weighed, dissolved in water, filtered through asbestos, the filtrate acidulated with 5 cc. diluted sulphuric acid warmed to about 60 C., treated with an excess of tenth-normal oxalic acid, and the excess of oxalic acid determined by titration with tenth-normal potassium permanganate.

Zinc Permanganate-Merck.—A brand of zinc permanganate-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.

ZINC PEROXIDE.—See Peroxides, Metallic.

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Cook Laboratories, Inc., 536 Lake Shore Drive, Chicago.—Typhoid Vaccine X Plain, 374; Typhoid Vaccine XX Combined, 374; Staphylococcus Vaccine (Combined), 371; Whooping Cough Vaccine X Plain, 368.

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Cutter Laboratory, Berkeley, Calif.—Acne Bacillus Vaccine, 366; Diphtheria Toxin-Antitoxin, Mixture, 0.1 L+, 356; Diphtheria Toxin for the Schick Test, 381; Diphtheria Toxoid, 364; Normal Serum (from the Horse), 341; Pollen Extracts, 31; Pollen Extracts Concentrated, 31; Polyanerobic Antitoxin, 343; Rabies Vaccine (Semple), 353; Scarlet Fever Streptococcus Antitoxin, 347; Silver Nitrate, Ampoule Solution, 1 per cent, 392; Special Pertussis Vaccine, 368; Staphylococcic Vaccine, 371; Tuberculin B. F. (Bouillon Filtrate), 363; Tuberculin for the Cutaneous Reaction (Pirquet's Reaction), 359; Tuberculin O. T. Bovine, 359; Tuberculin Old (Tuberculin O. T.), 359; Typhoid-Paratyphoid Prophylactic, 374; Typhoid Prophylactic, 374; Typhoid Vaccine, 374.

Davis & Geck, Inc., 211-221 Duffield St., Brooklyn, N. Y.—Kalmerid Germicidal Tablets Potassium Mercuric Iodide, 281.

DePree Company, Holland, Mich.—Sulpharsphenamine, 72; Sulpharsphenamine, 0.1, 0.15, 0.2, 0.3, 0.4, 0.45, 0.5, 0.6, 0.9, 1.0, 3.0 Gm. Ampules, 72.

Diarsenol Company, Inc., Buffalo, N. Y.—Diarsenol, 63; Diarsenol, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 1.0, 2.0, 3.0 Gm. Ampoules, 63; Neodiarsenol, 66; Neodiarsenol, 0.15, 0.3, 0.45, 0.6, 0.75, 0.9 Gm. Ampoules, 66; Sodium Diarsenol, 70; Sodium Diarsenol, 0.15, 0.3, 0.45, 0.6, 0.75, 0.9 Gm. Ampules, 70.

The Dick X-Ray Co., 3974-76 Olive St., St. Louis, Mo.—I-X Barium Meal, 87.

Dry Milk Co., 15 Park Row, New York, N. Y.—Protolac, 236.

Eastman Kodak Co., Rochester, N. Y. — Tetrabromophenolphthalein Sodium Salt, 163; Tetraiodophenolphthalein Sodium Salt, 164; Resorcinol Monoacetate, 329.

Efficiency Products Co., 25 Maple St., Somerville, N. J.—Hoffman's Non-Nutritive Nut Flour, 251.

Fairchild Bros. & Foster, Washington and Laight Sts., New York, N. Y.—B. Acidophilus Milk, 225; Bile Salts, 93; Enzymol, 132; Trypsin, 133.

Fritzsche Bros., Inc., 78-84 Beekman St., New York, N. Y.—Benzyl Benzoate, 90; Cypress, Oil of, 131.

Fougera, E. & Co., 44 Maiden Lane, New York, N. Y.—Lipiodol-Lafay, 208; Lipiodol-Lafay, Ampoules, 1, 2, 3, 5 cc., 208; Lipiodol Radiologique Ascendant, 209; Lipiodol Radiologique Descendant, 209.

Gallia Laboratories, Inc., 332 Broadway, New York, N. Y.—Arheol, 336; Arheol Capsules, 336; Cryogenine, 130; Cryogenine Tablets 0.5 Gm., 130; Riodine, 211; Riodine Capsules, 0.2 Gm. (3.1 grains), 211.

General Chemical Co., 40 Rector St., New York, N. Y.—Sofos, 393.

Gilliland Laboratories, Inc., Marietta, Pa.—Antimeningococcic Serum, 351; Antipneumococcic Serum Type I, 351; Bacillen Emulsion Tuberculin, "B.E.", 362; Bouillon Filtrate Tuberculin, "B.F.", 363; Diphtheria Toxin-Antitoxin Mixture, 0.1 L+, 356; Normal Horse Serum, 341; Original Tuberculin, "O.T.", 359; Pasteur Anti-Rabic Vaccine, 353; Pertussis Bacillus Vaccine, 368; Pirquet Test, 360; Rabies Vaccine (Semple Method), 353; Schick Test, 381; Staphylococcus Vaccine (Albus and Aureus), 371; Tuberculin Ointment in Capsules (for the Moro Percutaneous Diagnostic Test), 360; Tuberculin "O.T." (Old Tuberculin), 359; Typhoid-Paratyphoid Bacterial Vaccine Immunizing, 375; Typhoid Vaccine, 374.

Hart,, E. J. & Co., Ltd., 508-510 Chartres St., New Orleans La.—Lac Bismo, 99.

Hermes-Groves Dairy Co., Forbes St. at Sixth Ave., Pittsburgh, Pa.—Bacillus Acidophilus Milk-Hermes, 225.

Heilkraft Medical Co., 321 Talbot Ave., Boston, Mass.—Dimazon, 149; Dimazon Oil, 149; Dimazon Ointment, 149; Dimazon Powder, 149; Scarlet R Salve, 148; Scarlet R Medicinal-Kalle, 148.

Heyden Chemical Corporation, 50 Union Square, New York, N. Y.—Calomelol, 284; Calomelol Ointment, 284; Ichthynat, 396.

Hille Laboratories, 110 N. Franklin St., Chicago, Ill.—Lunosol, 390; Lunosol Capsules, 6 grains, 390.

Hoffmann-LaRoche Chemical Works, Nutley, N. J.—Betaine Hydrochloride-Roche, 190; Digalen-Roche (Cloetta), 135; Digalen-Roche (Cloetta), Ampules, 1.1 cc., 136; Digalen-Roche (Cloetta), Tablets, 136; Digalen-Roche (Cloetta), Hypodermic Tablets, 136; Homatropine Hydrochloride-Roche, 79; Iodostarine-Roche, 207; Iodostarine-Roche, Chocolate Tablets, 207; Iodostarine-Roche, Tablets, 0.25 Gm., 207; Isacen, 220; Isacen Tablets 0.005 Gm., 221; Larosan-Roche, 236; Oleo-Bi-Roche, 100; Oleo-Bi-Roche, Ampules, 2 cc., 101; Pantopon-Roche, 290; Pantopon-Roche (Pantopium Hydrochloricum) Ampules for Hypodermic Administration, 291; Pantopon-Roche (Pantopium Hydrochloricum) Hypodermic Tablets, 291; Pantopon-Roche (Pantopium Hydrochloricum) Tablets, 291; Papaverine Hydrochloride-Roche, 292; Papaverine Sulphate, 293; Papaverine Sulphate-Roche, Ampules, 293; Papaverine Sulphate Tablets-Roche, 0.04 Gm., 293; Theobromine and Sodium Acetate-Roche, 414; Thigenol, 398; Thiocol-Roche, 126; Thiocol-Roche, Syrup, 126; Thiocol-Roche Tablets, 5 grains, 126; Tyramine-Roche, 175; Scopolamine Stable-Roche, 337.

Hollister-Stier Laboratories, 477-482 Paulsen Medical and Dental Building, Spokane, Wash.—Acne Bacillus Vaccine, 366; Bacillus Acidophilus Culture, 224; Pertussis Bacillus Vaccine, 368; Pollen Extracts, 32; Staphylococcus Vaccine (Aureus and Albus), 372; Typhoid-Paratyphoid Vaccine (Prophylactic), 375.

Hoos, Louis, 5232 Kenmore Ave., Chicago, Ill.—Albumin Milk, Hoos, 259.

Horlick's Malted Milk Corporation, Racine, Wis.—Horlick's Maltose-Dextrin Milk Modifier, 245.

Hynson, Westcott & Dunning, Baltimore, Md.—Ampules Solution Antimony Sodium Thioglycollate, 0.5 per cent, 20 cc., 56; Ampules Solution Antimony Thioglycollamide, 0.4 per cent, 20 cc., 56; Antimony Thioglycollamide, 55; Antimony Sodium Thioglycollate, 56; Benzyl Benzoate, 90; Benzyl Benzoate, Globules of 90; Benzyl Benzoate, Miscible, Solution of, 90; Benzyl Benzoate, Sterile Ampules of, 90; Benzyl Succinate, Tablets of, 92; Bromsulphalein, 157; Bromsulphalein, Solution, 157; Flumerin, 264; Flumerin Tubes, 0.15, 0.20, 0.25, 0.30 Gm., 265; Glycotauro, 94; Glycotauro Capsules, 5 grains, 94; Glycotauro Capsules (half size), 94; Glycotauro, Enteric Coated, Tablets, 94; Mercurochrome-220 Soluble, 271; Mercurochrome-220 Soluble, Sealed Tubes, 0.5 Gm., 272; Mercurochrome-220 Soluble, Tablets of, 272; Mercury Biniodide Oil Solution in Ampules, 282; Mercury Salicylate, Sterile Ampules of, 1, 1½, 2 grains, 269 and 270; Meroxyl, 275; Meroxyl Tablets, 276; Ouabain Ampules, 143; Phenmethylol, 46; Phenmethylol Ampules, 1, 2, 4 per cent, 46; Phenolsulphonephthalein Ampules, 159; Phenoltetrachlorphthalein, 159; Phenoltetrachlorphthalein, Ampules, 160; Sterile Solution of Lutein, 296; Sterile Solution of Lutein, Ampules, 296.

Intarvin Company, 70 Jefferson St., New York, N. Y.—Intarvin, 263.

Jensen-Salsbery Laboratories, Inc., 21st and Penn Sts., Kansas City, Mo.—Rabies Vaccine (Human) Phenol Killed, 353.

Johnson & Johnson, New Brunswick, N. J.—Chlorine-Soda Ampoules, 192.

Kansas City Oxygen Gas Co., 2012 Grand Ave., Kansas City, Mo.—Ethylene for Anesthesia (Kansas City Oxygen Gas Company), 42.

Laboratory Products Co., Cleveland, Ohio.—Protein S. M. A. (Acidulated), 261.

Lederle Antitoxin Laboratories, Pearl River, Rockland Co., N. Y.—Acne Vaccine, 366; Anaerobic Antitoxin (Polyvalent), 343; Anti-Anthrax Serum, 349; Antidysenteric Serum (Polyvalent), 350; Antimeningococcic Serum, 351; Antipneumococcus Serum, Type 1, 351; Bacillus Acidophilus Milk, 226; Cholera Vaccine (Prophylactic), 367; Corpus Luteum Extract, 296; Corpus Luteum Extract, Ampules, 1 cc., 296; Corpus Luteum Extract, 5 cc. vial, 296; Diphtheria Toxin-Antitoxin Mixture (0.1 L+), 256; Erysipelas Streptococcus Antitoxin, Refined and Concentrated, 346; Intracutaneous Tuberculin for the Mantoux Test, 360; Normal Horse Serum, 341; Pertussis Glycerol-Vaccine, 368; Pertussis Vaccine for Prophylaxis, 368; Pertussis Vaccine for Treatment, 368; Plague Vaccine (Prophylactic), 370; Poison Ivy Extract (in Almond Oil), 330; Poison Ivy Extract (in Almond Oil) 1 cc., 330; Poison Oak Extract (in Almond Oil), 330; Poison Oak Extract (in Almond Oil) 1 cc., 330; Pollen Antigen, 28; Rabies Vaccine (Semple Method), 354; Scarlet Fever Streptococcus Antitoxin (Refined and Concentrated), 348; Schick Test, 381; Silver Nitrate, Ampule Solution, 1 per cent, 393; Staphylococcus Albus Vaccine, 372; Staphylococcus Aureus Vaccine, Polyvalent, 372; Staphylococcus Vaccine, 372; Thromboplastin, 184; Tuberculin "B. E.", 362; Tuberculin "B. F." (Bouillon Filtrate), 363; Tuberculin "O. T." (Old Tuberculin), 360; Tuberculin Pirquet Test ("T. O."), 360; Tuberculin Subcutaneous Test ("T. O."), 360; Typhoid Combined Vaccine (Prophylactic), 375; Typhoid Vaccine (for Prophylactic Treatment), 375.

Lilly, Eli, & Co., Inc., Indianapolis, Ind.—Antimeningococcic Serum Concentrated, 351; Chloroxyl, 118; Chloroxyl Tablets, 5 grains, 119; Cholera Vaccine, Prophylactic, 367; Coco-Quinine, 317; Ephedrine, 168; Ephedrine Compound, Inhalant, 168; Ephedrine Compound, Ointment, 168; Ephedrine Hydrochloride, 170; Ephedrine Hydrochloride, Hypodermic Tablets, 0.016 Gm. (¼ grain), 0.0325 Gm. (½ grain), 170; Diphtheria Toxin-Antitoxin Mixture, 0.1 L+, 357; Ephedrine Hydrochloride, Pulvules, ⅜, ¾ grain, 170; Ephedrine Hydrochloride, Solution, 3 per cent, 170; Ephedrine, Inhalant (Plain), 168; Ephedrine Jelly, 171; Ephedrine Sulphate, 171; Ephedrine Sulphate, Ampoules, 1 cc., 0.05 Gm., 172; Ephedrine Sulphate, Hypodermic Tablets, 0.016 Gm. (¼ grain), 0.0325 Gm. (½ grain), 171; Ephedrine Sulphate, Pulvules, 0.025, 0.05 Gm., 171 and 172; Ephedrine Sulphate, Syrup Nos. 110, 111, 172; Erysipelas Streptococcus Antitoxin (Concentrated Globulin), 346; Glucose (Dextrose, U. S. P.), Ampoules, 10 Gm., 20 cc.; 25 Gm., 50 cc.), 246; Iletin (Insulin-Lilly), 200; Iletin (Insulin-Lilly) U-10, U-20, U-40, (5 cc.), U-10, U-20, U-40, U-80, U-100 (10 cc.), 200; Invert Sugar, Solution of, 393; Invert Sugar, Solution of, 5, 6, 7.5 Gm. in 10 cc., 394; Liver Extract No. 343, 232; Merthiolate, 276; Merthiolate Solution 1:1,000, 276; Normal Horse Serum, 341; Old Tuberculin, Human Strain, Concentrated, 360; Oridine, 210; Oridine Tablets, 210; Ouabain, Ampoules, 0.0005 (1/128 grain), 143; Para-Thor-Mone, 299; Para-Thor-Mone, P-20, 5 cc., 300; Pasteur Antirabic Preventive Treatment (Harris Modification), 354; Pertussis Vaccine, 369; Pirquet Test, 360; Plague Vaccine, Prophylactic, 370; Ricinoleated Scarlet Fever Antigen Immunizing, 371; Scarlet Fever Streptococcus Antitoxin (Refined and Concentrated), 348; Schick Test, 381; Staphylococcus Aureus Vaccine, 372; Staphylococcus Vaccine, 372; Strophanthin, Hypodermic Tablets, 1/100, 1/120, 144; Tuberculin Ointment for the Moro Percutaneous Test, 360; Typhoid Mixed Vaccine, Prophylactic and Therapeutic, 376; Typhoid Vaccine, Prophylactic and Therapeutic, 375.

Lister Bros., Inc., 41 East 42nd St., New York, N. Y.—Lister's Casein-Palmnut Dietetic Flour, 241.

MacDowell Brothers, Ogdensburg, N. Y.—MacDowell's Wheat-Nut-Casein Dietetic Flour, 241.

Mallinckrodt Chemical Works, St. Louis. Mo.—Benzyl Benzoate, 91, Bromeikon, 163; Bromeikon, 5 Gm. Ampules, 163; Copper Citrate, 122; Iodeikon, 164; Iodeikon, 3.5 Gm. Ampules, 164; Iso-Iodeikon, 161; Iso-Iodeikon, 2.5 Gm. Ampoules, 161; Mercuric Cyanide, 258; Quinidine, 316; Sulpharsphenamine, 72; Sulpharsphenamine, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 Gm. Ampules, 72.

Maltbie Chemical Co., 246-250 High St., Newark, N. J.—Calcreose, 123; Calcreose, Compound Syrup of, 124; Calcreose, Solution, 124; Calcreose Tablets, 4 grains, 124.

Maltine Company, 8th Ave. and 18th St., Brooklyn, N. Y.—Maltine, 247; Maltine Ferrated, 220; Maltine with Cod Liver Oil, 255; Maltine with Cascara Sagrada, 112; Maltine with Creosote, 124; Malto-Yerbine, 179.

Manhattan Eyesalve Co., Louisville, Ky.—Butyn Ointment-M. E. S. Co., 48; Compound Yellow Oxide and Adrenalin Ointment, 284; Copper Citrate Ointment (5, 10 per cent), 122; Holocaine and Adrenalin Ointment-M. E. S. Co., 48; Holocaine Ointment-M. E. S. Co., 48.

Mead Johnson & Co., Evansville, Ind.—Casec, 236; Dextri-Maltose Nos. 1, 2, 3, 244; Dry Malt Soup Stock, 249; Powdered Boilable Protein Milk, 260; Powdered Lactic Acid Milk Non-Curdling, No. 1, with Dextri-Maltose, 260; Standardized Cod Liver Oil, 256; Standardized Cod Liver Oil, Flavored, 256; Sobee, 242; Viosterol in Oil, 100 D, 411.

Merck & Company, Rahway, N. J.—Agar-Agar Powder, 23; Agar-Agar Shreds, 23; Arbutin, 57; Arsenobenzol-Billon, 62; Arsenobenzol-Billon, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 Gm. Ampules, 62; Benzene (Benzol) Medicinal, "C. P." Crystallizable, 89; Benzyl Benzoate, 91; Benzyl Succinate, 92; Betanaphthol Benzoate, 287; Bismosol, 96; Bismosol Ampules, 1 cc., 96; Bromipin, 10 per cent, 103; Bromipin, 33 per cent, 104; Butyl-Chloral Hydrate, 115; Calcium Peroxide, 308; Calcium Phosphate Tribasic, 407; Cantharidin, 111; Copper Citrate, 123; Digitan, 145; Digitan Ampules (for Hypodermic Use), 145; Digitan Tablets, 1½ grain (0.1 Gm.), 145; Digitan Tincture, 145; Digitoxin, 142; Erythrol Tetranitrate, 289; Erythrol Tetranitrate Tablets, ½, ¼ grain, 289; Ethyl Salicylate, 334; Fluorescein, 156; Formin, 188; Formin Tablets, 5 grains (0.3 Gm.), 7½ grains (0.5 Gm.), 188; Homatropine Hydrochloride, 79; Iodipin 10 per cent, 205; Iodipin 10 per cent, Tablets, 206; Iodipin 40 per cent, 206; Iodipin 40 per cent, Ampules, 2 cc., 206; Iron Lactate, 219; Kelene, 40; Magnesium Phosphate Tribasic, 408; Mercury and Potassium Iodide, 282; Mercury Benzoate, 267; Mercury Cyanide, 268; Mercury Succinimide, 271; Novarsenobenzol-Billon, 66; Novarsenobenzol-Billon 0.15, 0.3, 0.45, 0.6, 0.75, 0.9 Gm. Ampules, 66; Optochin Base, 180; Optochin Base, Tablets, 2 grains, 180; Optochin Hydrochloride, 180; Ouabain (G. Strophanthin), 144; Papaverine Hydrochloride, 292; Phloridzin, 311; Quinidine, 316; Scarlet R. Medicinal Biebrich, 148; Silver Citrate, 392; Silver Lactate, 392; Skiabaryt for Oral Administration, 87; Skiabaryt for Rectal Administration, 88; Sodium Peroxide, 309; Stovarsol, 74; Stovarsol Tablets, 0.25 Gm., 74; Sulpharsphenamine-Billon, 72; Sulpharsphenamine-Billon, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 Gm. Ampules, 72; Theobromine, 413; Theobromine and Sodium Acetate, 414; Tryparsamide, 76; Urea, 409; Zinc Permanganate, 417.

Merrell-Soule Company, Syracuse, N. Y.—Powdered Protein Milk, 261.

Metz, H. A., Laboratories, Inc., 170 Varick St., New York, N. Y.—Alumnol, 39; Anaesthesine, 53; Benzosol, 125; Holocaine, 49; L-Suprarenin Synthetic Bitartrate, 174; L-Suprarenin Synthetic Bitartrate Tablets, 0.001 Gm., 174; Melubrin, 313; Neosalvarsan, 66; Neosalvarsan, Dose I, II, III, IV, V, VI, X, XII, XX, XXX, 66; Novocain, 50; Novocain and L-Suprarenin Synthetic Hypodermic Tablets "A", "B", "C", "E", "H", 50; Novocain Hypodermic Tablets "D", "F", "T", 50; Novocain Solution 1 per cent Ampules, 50; Pyramidon, 314; Orthoform, 54; Oscodal, 258; Oscodal Tablets, 259; Pyramidon Tablets, 5 grains, 314; Salyrgan, 282; Salyrgan Solution, Ampules, 1 cc., 283; Salvarsan, 63; Salvarsan, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 1, 2, 3 Gm. Tubes, 63; Silver-Salvarsan, 68; Silver Salvarsan 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.6 Gm. Ampules, 69; Sulpharsphenamine, 72; Sulpharsphenamine 0.05, 0.075, 0.1, 0.15, 0.3, 0.45, 0.6 Gm. Ampules, 73.

Monsanto Chemical Works, St. Louis, Mo.—Halazone, 195.

Morgenstern & Company, 454—18th St., Brooklyn, N. Y.—Cinchophen Tablets, 118; Cinchophen Water, 118; Perogen Bath, 306; Salophen, 310.

Mulford, H. K. & Co., Philadelphia, Pa.—Acidophilus Bacillus Liquid, 224; Acne Bacterin, 367; Acne Serobacterin (Sensitized Acne Vaccine Polyvalent), 380; Anterior Lobe Pituitary Extract, Sterile Solution of, 304; Anterior Lobe Pituitary Extract, Sterile Solution of, Ampules, 1 cc., 304; Anti-Anthrax Serum, 349; Antidysenteric Serum (Polyvalent), 350; Antimeningitis Serum, 351; Antipneumococcic Serum, Type I, 352; Antivenin (Bothropic), 344; Antivenin (Nearctic Crotalidae), 345; Bacillen Emulsion "B. E.", 362; Carbon Tetrachloride, Capsules, 0.3, 1, 3 cc., 112; Cargentos, 388; Cargentos Capsules, 3 grains, 388; Cargentos Ointment, 5, 10 per cent, 388; Cargentos Urethral Suppositories, 388; Cholera Bacterin (Cholera Vaccine), 367; Cholera Serobacterin (Sensitized Cholera Vaccine), 380; Cremo-Bismuth, 99; Digitol, 145; Digitos, 140; Digitos Ampules, 1, 5 cc., 140; Diphtheria Toxin-Antitoxin Mixture, New Formula (Park-Banzhaf's 0.1 L+), 357; Diphtheria Toxin for the Schick Test, 381; Diphtheria Toxoid, 365; Erysipelas Streptococcus Antitoxin (Concentrated), 346; Gelatin Compound Phenolized, 188; Insulin, 198; Insulin, 10, 20, 40 Units (5 cc.), 10, 20, 40, 80 Units (10 cc.), 198; Iodo-Casein, 205; Iodo-Casein Tablets, 5 grains (0.3 Gm.), 205; Iodo-Casein with Chocolate, Tablets, 205; Ivyol, 329; Ivyol, Hypo Units, 329; Krelos (Disinfectant), 128; Mercurial Ointment, Improved, 284; Mercurial Ointment, Improved, Capsules, 30, 60 grains, 285; Mercuric Succinimide, Hypodermic Tablets No. 50, 0.012 Gm. (⅕ grain), 270; Mercury Succinimide, Ampuls, ⅙ grain, 270; Mulford Acidophilus Bacillus Blocks, 229; Neorobin, 288; Neorobin, Vacuum Sealed Tubes, 1, 5 grains, 288; Normal Serum (from the Horse), 341; Normal Horse Serum Without Preservative, 341; Perfringens Antitoxin, 343; Pertussis Bacterin, 369; Pirquet Test for Tuberculosis, 360; Pirquet Test for Tuberculosis (Bovine Type), 360; Plague Bacterin, 370; Pneumococcus Antibody Solution, Types I, II and III Combined, 342; Pollen Extracts (Glycero-Saline), 34; Pollen Extracts, 33; Protan, 401; Protan and Opium Tablets, No. 1, 401; Protan, Friable Tablets, 5 grains, 401; Protein Extracts, 36; Purified Three Cresols, 127; Quinine, Syrup of, with Chocolate, 317; Rabies Vaccine, 354; Rabies Vaccine (Phenol Killed), 354; Scarlet Fever Streptococcus Antitoxin Concentrated, 348; Sodium Cacodylate, Ampules, ¾ grain (1 cc.), 1½ grains, 3 grains (1 cc.), 5 grains (1 cc.), 7¾ grains, 15 grains, 74; Staphylo-Serobacterin (Sensitized Staphylococcic Vaccine), 380; Tetanus Antitoxin (Bovine), 345; Tuberculin Filtrate, "B. F.", Denys, 363; Tuberculin Intracutaneous (Bovine Type), 361; Tuberculin Intracutaneous (Human Type), 360; Tuberculin Ointment (Moro Ointment), 360; Tuberculin Ointment (Moro Ointment) (Bovine Type), 360; Tuberculin "Old" (O. T.), 360; Tuberculin T. R., 361; Typho-Bacterin, 376; Typho-

Bacterin Mixed (Triple Vaccine TAB), 376; Typho-Serobacterin (Sensitized Triple Vaccine TAB), 380; Typho-Serobacterin (Sensitized Typhoid Vaccine), 380; Zinc Permanganate, Tablets, 1 grain, 416.

National Aniline & Chemical Company, 40 Rector St., New York, N. Y.—Acriflavine, 152; Gentian Violet Medicinal, 166; Gentian Violet Medicinal, Enteric Coated Tablets, 0.0324 Gm. (½ grain), 167; Gentian Violet Medicinal, Tablets, 0.0324 Gm. (½ grain), 166; Neutral Acriflavine, 153; Neutral Acriflavine, Enteric Coated Tablets, 0.0325 Gm. (½ grain), 153; Neutral Acriflavine Ointment, 1 per cent, 153; Neutral Acriflavine "Pro Injectione," 0.5, 1.0 Gm. vials, 153; Neutral Acriflavine, Tablets, 0.1 Gm. (1½ grains), 153; Neutral Acriflavine Troches, 153; Proflavine, 154; Scarlet Red Medicinal, 148.

National Drug Company, 5109 and 5111 Germantown Ave., Philadelphia, Pa.—Diphtheria Toxin-Antitoxin Mixture (Diphtheria Prophylactic), 357; Diphtheria Toxoid, 365; Normal Horse Serum, 341; Pertussis Vaccine, 369; Rabies Vaccine-Human (Semple Method), 354; Staphylococcus Vaccine, 372; Typhoid-Paratyphoid A Vaccine, 377; Typhoid-Paratyphoid Combined Vaccine, 376; Typhoid Vaccine, 376.

National Pathologic Laboratories, 601-616 University Club Building, St. Louis, Mo.—Rabies Vaccine (Harris), 353.

New York Quinine & Chemical Works, 99-117 North 11th St., Borough of Brooklyn, N. Y.—Quinidine, 316.

North, Horace, 513, 33d St., Brooklyn, N. Y.—Citresia, 121.

Norton, John Co., 30 North Washington Ave., Columbus, Ohio.—Dioprotein Prepared Casein Flour, 240.

Nutrivoid Products Co., Inc., 23 Cliff St., New York, N. Y.—Nutrivoid Flour, 252.

Ohio Chemical and Manufacturing Company, 1117-1199 Marquette St., N. E., Cleveland, Ohio.—Lennox Ethylene, 42.

Parke, Davis & Co., Detroit, Mich.—Adrenalin, 173; Adrenalin and Chloretone Ointment, 173; Adrenalin and Cocaine Tablets, 173; Adrenalin Chloride Solution, 173; Adrenalin Chloride Solution, Ampoules, ℞ 1, 1: 10,000, 1 cc., ℞ 2, 1: 2,600, 1 cc., 173 and 174; Adrenalin Chloride Solution 1:1,000, Ampoules, 1 cc., 174; Adrenalin Inhalant, 173; Adrenalin Ointment, 173; Adrenalin Suppositories, 173; Adrenalin Tablets, 173; Adrenalin Tablets No. 2, 173; Ampoules of Pitocin, 1 cc., 304; Ampoules of Pitocin, 304; Ampoules of Pitressin, 303; Ampoules of Pitressin, 1 cc., 303; Anti-Anthrax Serum, 349; Antidysenteric Serum, 350; Antimeningococcic Serum, 351; Antipneumococcic Serum, Type I, 352; Apothesine, 44; Apothesine and Adrenalin Hypodermic Tablets, 45; Apothesine and Adrenalin Hypodermic Tablets (℞ "B"), 45; Apothesine and Adrenalin Hypodermic Tablets Cylindrical (for pressure anesthesia), 45; Apothesine Hypodermic Tablets, 0.08 Gm. (1¼ Gr.), 45; Apothesine Ointment, 45; Apothesine Solution, 44; Bismuth Salicylate in Oil, 97; Bismuth Salicylate in Oil, Glaseptic Ampules, 1 cc., 97; Bismuth Sodium Tartrate, Ampoules, 2 cc., 97; Boro-Chloretone, 115; Brometone, 103; Brometone Capsules, 5 grains, 103; Carbon Tetrachloride (for Human Use), Capsules, 20 minims, 112; Chloretone, 115; Chloretone Capsules, 3, 5 grains, 115; Chloretone Inhalant, 115; Corpora Lutea Soluble Extract, 295; Corpora Lutea Soluble Extract, Ampoules, 1 cc., 295; Dibromin Capsules, 6 grains, 131; Dibromin, 131; Diphtheria Toxin-Antitoxin Mixture, 0.1 L+, 357; Diphtheria Toxin for Schick Test, 382; Diphtheria Toxoid, 365; Ephedrine Sulphate, 172; Ephedrine Sulphate, Capsules, 0.025 Gm. (⅜ grain), 0.05 Gm. (¾ grain), 172; Ephedrine Sulphate, Glaseptic Ampoules, 0.05 Gm. (¾ grain), 1 cc., 172; Ephedrine Sulphate, Solution, 3 per cent, 172; Ergot Aseptic, 177; Ergot Aseptic, Ampoules, 1 cc., 177; Erysipelas and Prodigiosus Toxins (Coley), 379; Erysipelas Streptococcus Antitoxin Refined and Concentrated, 346; Furunculosis Vaccine, 372; Glaseptic Ampoules, Sodium Cacodylate, 0.1 Gm. (1½ grains), 1 cc.; 0.13 Gm. (2 grains), 1 cc.; 0.2 Gm. (3 grains), 1 cc.; 0.3 Gm. (5 grains), 1 cc.; 0.45 Gm. (7 grains), 1 cc.; 1 Gm. (15½ grains), 2 cc., 75; Glaseptic Ampoules, Sodium Cacodylate (for Intravenous Use), 0.2 Gm. (3 grains), 5 cc.; 0.45 Gm. (7 grains), 5 cc.; 1 Gm. (15½ grains), 10 cc., 75; Glucose, Glaseptic Ampoules Solution, 50 per cent, 50 cc., 246; Iron Citrate Green, 219; Iron Citrate Green, Ampoules, ¼, ¾, 1½ grains, 219 and 220; Malt Extract with Cod Liver Oil, 257; Malt Extract (Unmedicated), 247; Mercurettes, 285; Mercurol, 273; Mercurosal, 273; Mercurosal Ampoules, 0.1 Gm., 274; Mercurosal Solution, 274; Mercurosal, ℞ 1 (Intravenous), 274; Mercurosal ℞ 2 (Intramuscular), 274; Mercury Salicylate, Glaseptic Ampoules, 0.065 Gm. (1 grain), 0.13 Gm. (2 grains), 269; Mercury Succinimide, Glaseptic Ampoules, 0.01 Gm. (⅛ grain), 270; Neo-Silvol, 390; Neo-Silvol, Capsules, 6 grains, 391; Neo-Silvol Ointment 5 per cent, 391; Neo-Silvol Vaginal Suppositories, 391; Normal Horse Serum, 341; Iodalbin and Mercurol Tablets, 204; Iodalbin Capsules, 5 grains, 204; Iodalbin, 204; Ovarian Residue Soluble Extract, 295; Ovarian Residue Soluble Extract, Ampoules, 1 cc., 295; Ovarian Substance Soluble Extract, 294; Ovarian Substance Soluble Extract, Ampoules, 1 cc., 294; Parke, Davis & Co.'s Viosterol in Oil 100 D, 411; Paroidin, 301; Paroidin, 5 cc., 301; Pertussis Immunogen, 369; Pertussis Vaccine, 369; Pituitrin, 304; Pituitrin, Ampoules, 0.5, 1 cc., 305; Potassio-Mercuric Iodide, Germicidal Discs, Nos. 1, 2, 281; Proposote, 125; Proposote Capsules, 5, 10 minims, 126; Rabies Vaccine (Cumming), 355; Sal-Ethyl, 334; Sal-Ethyl Capsules, 5 minims, 334; Scarlet Fever Streptococcus Antitoxin, 348; Scarlet Fever Streptococcus Toxin for Preventive Immunization, 364; Scarlet Fever Streptococcus Toxin for Skin Test, 383; Scarlet Red Emulsion 4 per cent, 148; Scarlet Red Ointment, 5, 10 per cent, 148; Scarlet Red Sulphonate, 148; Silver Nitrate, Capsules Solution, 1 per cent, 393; Silvol, 388; Silvol Bougies 5 per cent, 388; Silvol Ointment 5 per cent, 388; Standardized Cod Liver Oil, 256; Staphylococcus Vaccine (Combined), 373; Stearodine, 211; Stearodine Tablets, 211; Tetanus-Perfringens Antitoxin Refined and Concentrated, 344; Tuberculin B. E. (Concentrated), 362; Tuberculin B. E., Tablets, 362; Tuberculin B. F. (Human), 364; Tuberculin B. F. (Bovine), 364; Tuberculin Ointment for the Moro Test, 361; Tuberculin for the Ophthalmo-Reaction, 361; Tuberculin (Old) and Control for the Pirquet Test, 361; Tuberculin "Old" (Koch), 361; Tuberculin T. R., 361; Tuberculin T. R., Tablets, 363; Typhoid-Paratyphoid Vaccine (Prophylactic), 377; Typhoid Vaccine (Prophylactic), 377; Vaginal Suppositories Silvol 5 per cent., 388.

Parmele Pharmacal Co., 47 West Street, New York, N. Y.—Chinosol, 113; Chinosol Tablets, 114.

Pasteur Institute of St. Louis, 3514 Lucas Ave., St. Louis, Mo.—Antirabic Virus (Semple), 355.

Patch, E. L. Co., Stoneham Postoffice, Boston, Mass.—Patch's Flavored Cod Liver Oil, 257.

Petrolagar Laboratories, Inc., 536 Lake Shore Drive, Chicago.—Petrolagar, 230; Petrolagar (Unsweetened), 230; Petrolagar (with Milk of Magnesia), 230; Petrolagar (with Phenolphthalein), 231.

Physicians Diagnostic Laboratories, 3022 East 14th St., Oakland, Calif.—Concentrated Culture of Bacillus Acidophilus, 227.

Prophylacto Manufacturing Co., 227 West Erie St., Chicago, Ill.—Ephedrine Hydrochloride-Pemco, 170; Ephedrine Hydrochloride-Pemco, Capsules, ¼ grain, 170; Ephedrine Hydrochloride-Pemco, Capsules, 0.3 Gm., 170.

Pure Gluten Food Co., 90 West Broadway, New York, N. Y.—Hoyt's Gluten Special Flour, 241.

Radium Chemical Company, 511 Fifth Ave., New York, N. Y.—Radium Bromide-Radium Belge, 325; Radium Carbonate-Radium Belge, 326; Radium Sulphate-Radium Belge, 326.

Radium Emanation Corporation, 250 West 57th St., New York, N. Y. —Radon, 327.

Radon Co., Inc., 1 East 42d Street, New York, N. Y.—Radon, 327.

Reinschild Chemical Company, 41 East 42nd St., New York, N. Y.—Phenolphthalein-Agar, 23.

Riedel & Company, Barry and South 5th St., Brooklyn, N. Y.—Mergal, 274; Ovogal, 94; Ovogal Capsules, 94; Salipyrin, 312; Salipyrin Tablets, 7½ grains, 312.

Roessler & Hasslacher Chemical Company, 10 East 40th St., New York, N. Y.—Calcium Peroxide, 308; Sodium Dioxide, Dental, 308; Sodium Peroxide, 309; Oxone, 309.

Sandoz Chemical Works, Inc., 61-63 Van Dam St., New York, N. Y.—Calcium Gluconate, 109; Calcium Gluconate, Ampules, 109; Gynergen, 177; Gynergen, Ampules, 1 cc., 178; Gynergen, Tablets, 0.001 Gm., 178.

Sargent's Drug Store, 23 N. Wabash Ave., Chicago, Ill.—Petrobran, 309.

Schering & Glatz, Inc., New York, N. Y.—Camiofen Ointment, 110; Collargol, 388; Collargol Ointment, 389; Digitalis Dispert, 146; Digitalis Dispert Tablets, 0.08 Gm., 146; Formalin, 187; Iocamfen, 201; Orphol-von Heyden, 97; Xeroform, 99.

Searle, G. D. & Co., 4737-4743 Ravenswood Ave., Chicago, Ill.— Bismuth Sodium Tartrate, Solution, 1.5 per cent, 97; Bismuth Sodium Tartrate, Ampoules, 2 cc., 97; Sulpharsphenamine, 73; Sulpharsphenamine, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 Gm. Ampules, 73.

Seydel Chemical Company, 135 Halladay St., Jersey City, N. J.—Benzyl Alcohol, 46; Benzyl Benzoate, 91; Benzyl Succinate, 92; Betanaphthol Benzoate, 287; Mercury (Mercuric) Benzoate, 267.

Sharp & Dohme, Baltimore, Md.—Caprokol, 328; Caprokol (Hexylresorcinol), Capsules, 0.15 Gm., 328; Caprokol (Hexylresorcinol), 2½ per cent Solution in Olive Oil, 328; Cresatin, 129; Hexylresorcinol Solution S. T. 37, 328; Strophanthin, Hypodermic Tablets, 1/200 grain (0.325 mg.), 144.

Squibb, E. R. & Sons, 80 Beekman St., New York, N. Y.—Acne Vaccine, 367; Antimeningococcic Serum, 351; Antipneumococcic Serum, Type I, 352; Bacillus Bulgaricus, 226; Cod Liver Oil, 255; Diphtheria Toxin-Antitoxin Mixture (New Formula), 357; Diphtheria Immunity Test (Schick Test), 382; Diphtheria Toxin-Antitoxin Mixture (New Formula) (Sheep), 357; Diphtheria Toxoid, 366; Ephedrine Hydrochloride, 170; Ephedrine Hydrochloride, Tablets, ⅜, ¾ grain, 170; Erysipelas Streptococcus Antitoxin Concentrated, 347; Insulin, 199; Insulin, 10, 20, 40 units (5 cc.), 10, 20, 40, 80, 100 units (10 cc.), 199; Ipral, 84; Ipral Tablets, 2 grains, 84; Mercuric Salicylate, Ampules, 0.065 Gm., 269; Normal Horse Serum, 341; Parathyroid Hormone, 300; Parathyroid Hormone, 5 cc., 300; Pasteur Antirabic Vaccine, 355; Pertussis Vaccine, Immunizing, 369; Pertussis Vaccine, Curative, 369; Pollen Allergen Solutions, 27; Protargentum, 387; Protargentum, Tablets, 4.6 grains, 387; Rabies Vaccine (Semple Method), 355; Scarlet Fever Streptococcus Antitoxin Concentrated, 348; Scarlet Fever Streptococcus Toxin, 364; Scarlet Fever Streptococcus Toxin for Dick Test, 383; Sodium Cacodylate, Ampuls, 0.05, 0.13 Gm., 74; Solargentum, 388; Solargentum, Tablets, 4.6 grains, 388; Squibb's Cod Liver Oil with Viosterol 5 D, 258; Squibb's Cod

Liver Oil with Viosterol 5 D, Mint-Flavored, 258; Squibb's Liquid Petrolatum with Agar, 231; Squibb's Mint-Flavored Cod-Liver Oil, 255; Squibb's Vitavose, 249; Staphylococcus Vaccine, 373; Sulpharspenamine, 73; Sulpharsphenamine-Squibb, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.9, 3 Gm. Ampules, 73; Thromboplastin, 185; Thromboplastin Hypodermic, 185; Thyroxin Crude, 405; Thyroxin Tablets, 0.2, 0.4, 0.8, 2.0 mg., 405; Typhoid Vaccine, Curative, 377; Typhoid Vaccine (Immunizing), 377; Typhoid Vaccine Combined, Immunizing, 377; Viosterol in Oil 100 D, 411.

Stearns, Frederick & Co., Detroit, Mich.—Insulin, 199; Insulin, 10, 20, 40 Unit (5 cc.), 10, 20, 40, 80 Unit (10 cc.), 199.

Swan-Myers Company, Indianapolis, Ind.—Concentrated Pollen Extracts-Swan-Myers, 26; Dextrose 50 per cent, Ampoules, 20, 50 cc., 245; Ephedrine, 168; Ephedrine Hydrochloride, 170; Ephedrine Hydrochloride, Ampoules, 0.05 Gm., 1 cc., 170; Ephedrine Hydrochloride, Capsules, 0.025 Gm., 0.0324 Gm. (½ grain), 0.05 Gm., 170; Ephedrine Hydrochloride, Syrup, 170; Ephedrine Hydrochloride, Solution, 3 per cent, 170; Ephedrine Hydrochloride, Syrup (Double Strength), 170; Ephedrine Inhalant, 168; Iodeikon Capsules, 164; Mercuric Potassium Iodide, Sterile Ampoules, 0.016 Gm. (¼ grain), 281; Mercury Benzoate 2 per cent, Sterile Ampoules, 1 cc., 266; Mercury Biniodide, Sterile Ampoules, 0.01 Gm. (⅙ grain) in Oil, 282; Mercury Oxycyanide, Sterile Ampules of, 0.008, 0.016, 0.01 Gm., 268; Mercury Salicylate, Sterile Ampoules, 0.065 Gm. (1 grain), 0.097 Gm. (1½ grain), 269; Mercury Succinimide, Sterile Ampoules, 0.01 Gm. (⅙ grain), 270; Mixed Furunculosis Bacterin, 373; Pertussis Bacterin (Prophylactic), 369; Pollen Extracts, 35; Staphylococcus Bacterin, 373; Typhoid Bacterin (Prophylactic), 378; Typhoid-Paratyphoid Bacterin (Prophylactic), 378.

Synthetic Drug Company, 243 College St., Toronto 2, Canada.—Mercury Salicylate, Compressible Capsules 1, 1½, 2 grains, for Intramuscular Injection, 269.

Tailby-Nason Company, 4 Carlton St., Kendall Square Station, Boston, Mass.—Palatable Cod Liver Oil, Nason's, 256.

Takamine Corporation, 120 Broadway, New York, N. Y.—Hirathiol, 395.

Tappan Zee Surgical Co., Nyack, N. Y.—Causticks, Caustick Applicators and Special Caustick Applicators, 393; Cupricsticks, Cupric Applicators and Special Cupric Applicators (Copper Sulphate 20-25 per cent), 123; Iodosticks, Iodoapplicators and Special Iodoapplicators (Iodine 60 per cent and Potassium Iodide 40 per cent), 201; Stypsticks, Stypstick Applicators and Special Stypstick Applicators (Alum 75 per cent, and Potassium Nitrate 25 per cent), 39.

Towt-Nolan Laboratory, 2599 Grove St., Oakland, Calif.—Lactobacillus Acidophilus Milk (Towt), 228.

Thompson's Malted Milk Co., Waukesha, Wis.—Thompson's Maltose and Dextrin, 250.

Terrell's Laboratories, Medical Arts Building, Fort Worth, Texas.—Rabies Vaccine (Phenolized), 355.

United Laboratories, Inc., 327 South Fair Oaks Ave., Pasadena, Calif.—Culture Bacillus Acidophilus, 228.

United States Standard Products Company, Woodworth, Wis.—Acne Vaccine, 367; Diphtheria Toxin-Antitoxin Mixture, 0.1 L+, 357; Diphtheria Toxin-Antitoxin Mixture 0.1 L+ Non-Sensitizing (Goat), 357; Diphtheria Toxin for Schick Test and Control, 382; Normal Horse Serum, 341; Pertussis (Whooping Cough) Vaccine, 370; Rabies Vaccine (Semple Method), 355; Scarlet Fever Streptococcus Antitoxin, 348; Staphylococcus Combined Vaccine, 373; Typhoid Paratyphoid Vaccine Combined, 378; Typhoid Vaccine, 378.

Vitalait Laboratory of California, 327-333 South Fair Oaks Ave., Pasadena, Calif.—Vitalait Culture Bacillus Acidophilus, 229.

Waukesha Health Products Co., Waukesha, Wis.—Hepco Dodgers, 240; Hepco Flour, 240; Hepco Grits, 241.

Werner Drug & Chemical Company, 941 Race St., Cincinnati, Ohio. —Phenacaine, 49.

West Disinfecting Co., Long Island City, N. Y.—Phenoco, 128.

Wilson Laboratories, 4221-25 South Western Ave., Chicago, Ill.—Corpora Lutea Soluble Extract, 295; Corpora Lutea Soluble Extract, Ampoules, 1 cc., 295.

Winthrop Chemical Company, Inc., 170 Varick St., New York, N. Y. —Adalin, 106; Adalin Tablets, 5 grains (0.3 Gm.), 106; Agurin, 414; Alypin, 43; Ampules Luminal-Sodium (Powder), 2 grains, 83; Aristol, 202; Creosoial, 124; Chaulmestrol, 113; Chaulmestrol, Ampules, 1, 3 cc., 113; Cymarin, 142; Cymarin Solution, Ampules, 142; Cymarin, Tablets, 142; Duotal, 125; Elixir of Veronal, 81; Ferro-Sajodin, 212; Ferro-Sajodin Tablets, 8 grains, 212; Homocamfin, 188; Homocamfin, Ampules 10 per cent (for Intramuscular Use), 189; Homocamfin, Ampules, 1 per cent (for Intravenous Use), 189; Iothion, 213; Iothion Oil, 213; Luminal-Sodium, 83; Luminal Sodium Tablets, 1½ grains, 83; Luminal, 83; Luminal Capsules, 1½ grains, 83; Luminal Tablets, ¼, ½, 1½ grains, 83; Mesotan, 335; Mesurol, 100; Mesurol, Emulsion, 20 per cent, 100; Novaspirin, 333; Novaspirin Tablets, 5 grains, 334; Novasurol, 278; Novasurol Ampules, 279; Phanodorn, 86; Phanodorn Tablets, 3 grains, 86; Protargol, 387; Sabromin, 106; Sabromin Tablets, 8 grains, 106; Sajodin, 212; Sajodin Tablets, 1, 8 grains, 212; Salophen, 310; Salophen, Winthrop Tablets of, 310; Solarson, 75; Solarson Ampules, 1.2 cc., 75; Spirosal, 335; Tablets Tutocain, Nos. 1, 2, 3, 4 (with Suprarenin), 52; Tablets Tutocain, Nos. 5, 6, 52; Tannigen, 401; Theocin, 415; Theocin Soluble, Tablets, 2½ grains, 415; Tutocain, 51; Veronal, 81; Veronal-Sodium Tablets, 5 grains, 82; Veronal-Sodium, 82; Veronal Tablets, 5 grains, 81.

EXEMPTED ARTICLES

List of Articles Examined and Found Not to be Within the Scope of New and Nonofficial Remedies

Exempted Medicinal Articles: Articles which have been examined by the Council, which are marketed under descriptive, nonproprietary names with well established therapeutic claims, and which, therefore, are held by the Council not to require inclusion in New and Nonofficial Remedies:

ABBOTT LABORATORIES

Amidopyrine-Abbott
Arsphenamine-D. R. L.
Barbital-Abbott
Barbital Sodium-Abbott
Chlorcosane-Abbott
Cinchophen-Abbott
Dichloramine-T (Abbott)
Epinephrin-Abbott
Epinephrin Chloride Solution-Abbott
Neoarsphenamine-D. R. L.
Pituitary Solution-U. S. P.

ARMOUR & CO.

Pituitary Liquid (Obstetrical)-Armour

BENZOL PRODUCTS CO.

Cinchophen-B. P. C.

GEO. W. BRADY & CO.

Barium Sulphate-Brady for Roentgen-Ray Work

CALCO CHEMICAL CO.

Cinchophen-Calco

CUTTER LABORATORY

Diphtheria Antitoxin Concentrated
Glycerinated Vaccine Virus
Tetanus Antitoxin Concentrated

DE PREE LABORATORIES, INC.

Arsphenamine-De Pree
Neo-Arsphenamine-De Pree

FARWELL & RHINES CO.

F. & R.'s Genuine 80 Per Cent Gluten Flour

GANE & INGRAM, INC.

Phenobarbital U. S. P. (Gane & Ingram)

GILLILAND LABORATORIES, INC.

Gilliland's Concentrated and Refined Diphtheria Antitoxin
Gilliland's Concentrated and Refined Tetanus Antitoxin
Smallpox Vaccine

HEYDEN CHEMICAL CORPORATION

Acetylsalicylic Acid-Heyden

HYNSON, WESTCOTT & DUNNING

Phenolsulphonephthalein-H. W. & D.

KINGS COUNTY PACKING CO.

California Apricots (Sac-A-Rin Brand)
California Bartlett Pears (Sac-A-Rin Brand)
California Muscat Grapes (Sac-A-Rin Brand)
California Royal Anne Cherries (Sac-A-Rin Brand)
California Tidbits Hawaiian Pineapple (Sac-A-Rin Brand)
California Seedless Grapes (Sac-A-Rin Brand)
California Yellow Cling Peaches (Sac-A-Rin Brand)
California Whole Ripe Kadota Figs (Sac-A-Rin Brand)

LAKESIDE LABORATORIES, INC.

Ampoule No. 64 Calcium Chloride 1%.

LEDERLE ANTITOXIN LABORATORIES

Concentrated Tetanus Antitoxin (Globulin)
Diphtheria Antitoxin
Solution Epinephrine-Lederle
Thyroid Desiccated-Lederle
Tincture Digitalis-Lederle
Vaccine Virus

ELI LILLY & CO.

Diphtheria Antitoxin-Lilly (Purified, Concentrated)
Pituitary Extract-Lilly (Obstetrical)
Tetanus Antitoxin
Vaccine Virus

MALLINCKRODT CHEMICAL WORKS

Acetylsalicylic Acid-Mallinckrodt
Arsphenamine-Mallinckrodt
Barbital-Mallinckrodt
Barium Sulphate Pure-Mallinckrodt
Cinchophen-Mallinckrodt
Neoarsphenamine - Mallinckrodt
Quinidine Sulphate-Mallinckrodt
Quinine Ethyl Carbonate-Mallinckrodt
Sodium Acid Phosphate (Monobasic)-Mallinckrodt

MERCK & CO.

Acetylsalicylic Acid-Merck
Agar Agar-Merck
Barbital-Merck
Barbital Sodium-Merck
Barium Sulphate-Merck for X-Ray Diagnosis
Liquid Petrolatum-Merck
Quinidine Sulphate-Merck
Quinine Ethyl Carbonate-Merck
Sodium Phosphate Monobasic-Merck
Trioxymethylene-Merck

WM. S. MERRELL COMPANY

Acid Salicylic-Merrell
Sodium Salicylate-Merrell
Natural Oil of Sweet Birch-Merrell
Pituitary Extract Obstetrical-Merrell

MONSANTO CHEMICAL WORKS

Acetylsalicylic Acid (Aspirin)-Monsanto
Chloramine-T (Monsanto)
Chlorcosane-Monsanto
Dichloramine-T (Monsanto)

MORGENSTERN & CO.

Cinchophen-Morgenstern

H. K. MULFORD CO.

Diphtheria Antitoxin Superconcentrated
Glycerinated Vaccine Lymph
Granular Effervescent Caffeine and Potassium Bromide Comp.-Mulford
Pollens Dried-Mulford
Proteins Dried-Mulford
Solution Pituitary Extract-Mulford
Tetanus Antitoxin

NATIONAL DRUG CO.

Pollen Extracts Diagnostic

NEW YORK CITY DEPARTMENT OF HEALTH

Antitetanic Globulin Refined and Concentrated
Diphtheria Antitoxin (Globulin)

NEW YORK QUININE & CHEMICAL WORKS

Euquinine-N. Y. Q.
Quinidine Sulphate-N. Y. Q.

OHIO CHEMICAL & MANUFACTURING CO.

Lennox CO_2-Ether (Haggard)

PARKE, DAVIS & CO.

Bismuth Paste (Surgical)-P. D. & Co.
Diphtheria Antitoxin (Concentrated Antidiphtheric Serum Globulin)
Tetanus Antitoxin Globulin
Vaccine Virus

E. L. PATCH & CO.

Sugar of Milk (E. L. Patch & Co.)

PROPHYLACTO MANUFACTURING CO.

Pemco Menthol Eucalyptus Compound Nasal Spray

ROBINSON-PETTET CO.

Solution of Albuminate of Iron (Robinson-Pettet Co.)
Robinson's Lime Juice and Pepsin
Elixir Paraldehyd (Robinson-Pettet Co.)

WILLIAM RYDBERG BAKING CO.

Mansfield Agar Agar Wafers

G. D. SEARLE & CO., INC.

Arsphenamine-Searle
Neoarsphenamine-Searle

SEYDEL CHEMICAL CO.

Benzocaine-Seydel

SHARP & DOHME

Tincture Digitalis, Purified, S. & D. (Fat-Free)

SWAN-MYERS CO.

Phenobarbital Tablets, ¼ grain
Phenobarbital Tablets, ½ grain
Phenobarbital Tablets, 1½ grain

UPSHER SMITH CO.

Capsules Folia-Digitalis (Upsher Smith)
Capsules Folia-Digitalis (Upsher-Smith), ½ grain
Tincture Digitalis (Upsher Smith)
Tablets Folia-Digitalis (Upsher Smith)

E. R. SQUIBB & SONS

Acetylsalicylic Acid-Squibb
Arsphenamine-Squibb
Barium Sulphate-Squibb for Roentgen-Ray Work
Chloramine-T (Squibb)
Liquid Petrolatum Heavy (California)-Squibb
Neoarsphenamine-Squibb
Pituitary Solution-Squibb
Purified Diphtheria Antitoxin (Antidiphtheric Globulin)
Smallpox (Variola) Vaccine (Glycerinated)
Sodium Acid Phosphate-Squibb
Tetanus Antitoxin, Purified
Thyroxin (Squibb)

UNITED STATES STANDARD PRODUCTS CO.

Diphtheria Antitoxin Refined and Concentrated
Tetanus Antitoxin

W. T. WAGNER'S SONS CO.

Wagner's Artificial Vichy
Wagner's Artificial Vichy Citrated

WILSON LABORATORIES

Epinephrin-Wilson
Epinephrin Powder-Wilson
Epinephrin Solution 1:1,000-Wilson
Pituitary Solution U. S. P. X Obstetrical-Wilson

Exempted Nonmedicinal Articles.—Articles which have been examined by the Council, which are not advertised as therapeutic agents, the composition of which is sufficiently disclosed to permit judgment as to their harmlessness or safety, and the use of which under ordinary circumstances is, in the opinion of the Council, not contrary to the public welfare:

BARD-PARKER CO.

Bard-Parker Formaldehyde Germicide

JELLO CO., INC.

D-Zerta

JOHNSON & JOHNSON

K-Y Lubricating Jelly

NONSPI CO.

Nonspi

ARTICLES "DESCRIBED" BUT NOT ACCEPTED

In this department, proprietary articles are described which are not acceptable for inclusion in New and Nonofficial Remedies because unwarranted claims are made for them. Should the manufacturer modify these claims or submit evidence proving them, the preparations will be acceptable to New and Nonofficial Remedies.

STANOLIND SURGICAL WAX.—A brand of paraffin for films, melting at 47 C., being pliable at or below 25 C., and ductile at or below 29 C. Stanolind Surgical Wax was transferred from the body of New and Nonofficial Remedies to the "Described But Not Accepted" department of the book because it was marketed in such a way as to advertise an unaccepted article, that is, a circular advertising the unaccepted article was included within the trade package of Stanolind Surgical Wax. The Council urged the Standard Oil Company to revise its advertising so as to permit the continued recognition of the product, but the firm would make no definite promise as to the time of the withdrawal of the objectionable advertising.

Actions, Uses and Application.—See general article on Paraffin for Films (Surgical Paraffin, Plastic Paraffin).

Manufactured by the Standard Oil Company (Indiana), Chicago.

BIBLIOGRAPHICAL INDEX TO PROPRIETARY AND UNOFFICIAL ARTICLES NOT INCLUDED IN N.N.R.

The references given below include: first, the date of original publication of the article in *The Journal A. M. A.*, if it appeared there; and, second, for the benefit of those that do not have access to files of *The Journal*, the place where the description may be found in other publications: "Reports of the Council on Pharmacy and Chemistry," "Propaganda for Reform," volumes 1 and 2, and "Reports of the A. M. A. Chemical Laboratory." Some descriptions have appeared in THE JOURNAL but not in the reports and vice versa. Council Reports include reports on articles that have been considered by the Council, either at the request of the manufacturers or on the Council's own initiative. The names of the manufacturers (or their agents) follow the names of the preparations, except in those instances in which a drug is discussed in general, without reference to the product of any particular manufacturer.

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